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(54) Title: PHARMACEUTICAL COMPOUNDS

$$A—(B)_{b0}—C\text{-}N(O)_s \qquad (I)$$

$$A—C(—B_1)(—N(O)_s) \qquad (II)$$

(57) Abstract

Steroidal compounds or their salts having general formulas (I) and (II) wherein: s is an integer equal to 1 or 2, preferably s = 2; b0 = 0 or 1; A = R–, wherein R is the steroidal drug radical, C and C_1 are two bivalent radicals. The precursors of the radicals B and B_1 are such as to meet the pharmacological tests reported in the description.

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"PHARMACEUTICAL COMPOUNDS"

* * * * * *

The present invention relates to novel steroidal compounds for systemic use and non systemic use, and their compositions, to be used in the conditions of oxidative stress and/or endothelial dysfuntions. Specifically it relates to compounds with a steroidal structure having antiinflammatory, immunodepressive and angiostatic activity (the so called antiinflammatory steroids), or gastrointestinal activity.

The compounds according to the present invention result therapeutically useful in the treatment of morbid conditions wherein the steroidal products are generally used with greater benefit, in terms both of a better tolerability and/or efficacy.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and of that of the surrounding tissue (Patho-physiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions are meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can bring about a series of pathological processes affecting various organs and

body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very ofthen typical of the elderly. As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.

- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower efficacy and/or higher toxicity.

This happenss for example with steroids.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

It is well known that steroids represent a first choice pharmacological intervention in the therapy of inflammatory diseases. This class of drugs, among which can be mentioned for example hydrocortisone, cortisone, prednisone, prednisolone, fludrocortisone, desoxycorticosterone, metilprednisolone,

triamcinolone, paramethasone, betamethasone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, beclomethasone, acetoxypregnelone, etc., elicits remarkable pharmaco-toxicological effects on different organs, and for this reason both their clinical use and its interruption cause a series of side effects, some of which very serious. See for example Goodman & Gilman, "The pharmaceutical Basis of Therapeutics" 9th ed., pages 1459-1465, 1996.

Among said toxic effects can be mentioned those affecting the bone tissue leading to an altered cellular metabolism and an high osteoporosis incidence; those affecting the cardiovascular system, generating an hypertensive response; those affecting the gastrointestinal apparatus giving gastric damages.

See for example Martindale "The extrapharmacopoeia", 30th ed., pages 712-723, 1993.

To the class of steroidal drugs belong also biliary acids, that have been used in the therapy of hepatic disorders and in biliary colics. Ursodesoxycholic acid is also used in some hepatic dysfunctions (hepatic cirrhosis of biliary origin, etc.). Their tolerability is strongly worsened in the presence of gastrointestinal complications (chronic hepatic damage, peptic ulcer, intestinal inflammation, etc.). Also in the case of biliary acids the oxidative stress remarkably affects drug performance: both the efficacy and the tolerability of

chenodeoxycholic and ursodesoxycholic acids are significantly reduced. In particular the unwanted effects on liver are found exalted. Among the steroidal compounds can be mentioned also estrogens for the treatment of dislipidaemias, hormonal troubles, female apparatus tumours treatment can be mentioned. Also said steroids show side effects as above mentioned, in particular at the hepatic level.

According to the above mentioned prior art it seems almost impossible to separate therapeutic activity from side effects, see Goodman et al, above mentioned, at p. 1474.

The steroidal compounds are completely different from the antiinflammatory non steroidal compounds from the chemical, pharmacological and biochemical point of view, since the pharmaco-toxicological mechanism of action of nonsteroidal antiinflammatory products is based on the inhibition of one or more of the cyclooxygenases (COX), while steroids do not influence COX and have more complex pharmaco-toxicological mechanisms of action not yet fully cleared.

Indeed it is well known that these two groups of drugs are classified in different classes in the pharmacopoeias.

The need was felt to have available steroids showing an improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions, without showing the

drawbacks of the drugs of the prior art.

It has been now surprisingly and unexpectedly found that the aforementioned technical problems shown in the administration of steroidal drugs to patients affected by oxidative stress and/or endothelial dysfunctions, or to the elderly in general, are solved by a new class of drugs as described hereinafter.

An object of the invention are steroidal compounds or their salts having the following general formulas (I) and (II):

$$A—(B)_{b0}—C\text{-}N(O)_s \qquad (I)$$

wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

b0 = 0 or 1;

A = $R—T_1$-, wherein R is the steroidal drug radical as defined hereunder,

B = -$T_B—X_2—T_{BI}$- wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when the reactive function in the precursor steroid is -OH; T_B = X when the reactive function in the precursor steroid is -COOH;

X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl having from 1 to 5 carbon atoms, or a free valence;

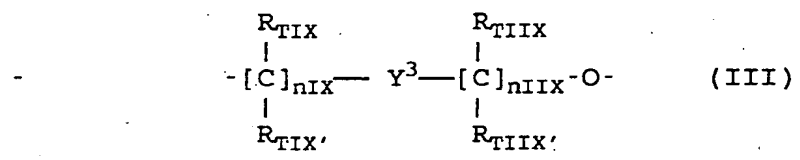
T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0, tx = 0 when txx = 1; X is as above defined;

X_2 is a bivalent bridging bond as defined hereunder;

C is the bivalent radical $-T_c-Y-$ wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is:



(III)

wherein:

nIX is an integer between 0 and 3, preferably 1;

nIIX is an integer between 1 and 3, preferably 1;

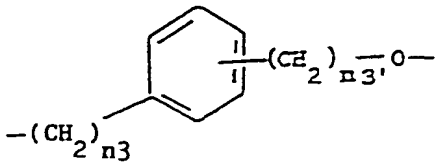
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, preferably one or two nitrogen atoms, said ring having 5 or 6 atoms.

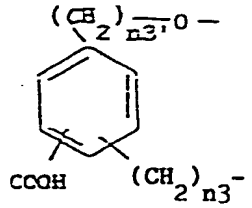
or Y is Y_0, selected from the following:

- an alkylenoxy group R'O wherein R' is linear or branched when possible C_1-C_{20}, preferably having from 1 to 6 carbon atoms, most preferably 2-4 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be substituted with heteroatoms, the ring

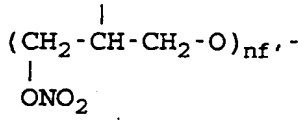
can have side chains of R' type, R' being as above defined; or

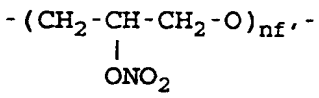


wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

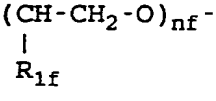


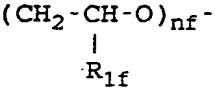
wherein n3 and n3' have the above mentioned meaning





wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



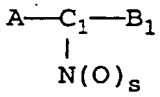


wherein R_{1f} = H, CH_3 and nf is an integer from 1 to

6; preferably from 1 to 4;

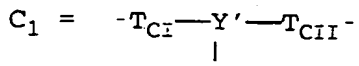
preferably Y = $-Y_0$ = R'O- wherein R' is as above defined;

preferably R' is a C_1-C_6 alkylene;



(II)

wherein:

C_1 = 

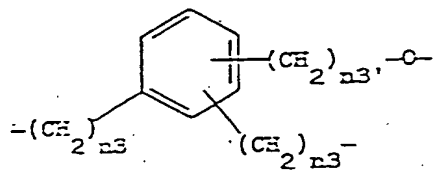
wherein T_{CI} and T_{CII} are equal or different,

T_{CI}= (CO) when the reactive function of the precursor steroid is -OH, T_{CI} = X when the reactive function of the precursor steroid is -COOH, X being as above defined;

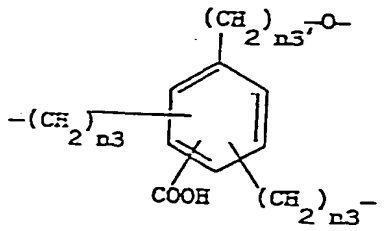
T_{CII}= $(CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that tI = 1 when tII = 0; tI = 0 when tII = 1; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably it is selected from the following:

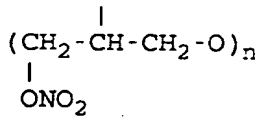
- a -R'O- group wherein R' is linear or branched C_1-C_{20}, preferably having from 1 to 6 carbon atoms, most preferably 2-4, or a saturated, optionally substituted, ring having from 5 to 7 carbon atoms; or



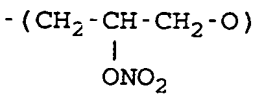
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



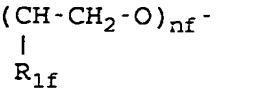
wherein n3 and n3' have the above mentioned meaning;



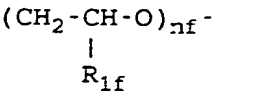
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom

on one of the carbon atoms is substituted by a free valence;

preferably Y' = - R'O- wherein R' is a linear or branched C_2-C_4, the oxygen which in Y' is covalently linked to the $-N(O)_s$ group is at the end of the free bond indicated in C_1 formula;

or Y' = Y_0 as defined in (I) but with three free valences instead of 2;

B_1 = $-T_{BII}—X_{2a}$

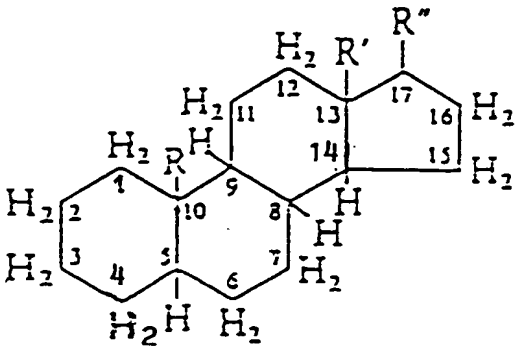
wherein X_{2a} is a monovalent radical,

T_{BII} = (CO) when tI = 0, T_{BII} = X when tII = 0, X being as above defined;

- X_2, bivalent radical, is such that the corresponding precursor of B: $-T_B—X_2—T_{B'}-$ meets test 4 or test 5, precursor in which the T_B and $T_{B'}$ free valences are each saturated with OZ, with Z or with $-Z^I-N(Z^{II})-$, Z^I and Z^{II} being equal or different and have the Z values as above defined, depending on whether T_B and/or $T_{B'}$ = CO or X, in connection with the values of t, t', tx and txx;
- the C precursor when b0 = 0 is of $-T_C$-Y-H type wherein the T_C free valence is saturated with OZ, Z, or with $-Z^I-N(Z^{II})-$, Z^I and Z^{II} being as above defined and is such as to meet test 5;
- X_{2a} monovalent radical, such that the corresponding

precursor of B_1 -T_{BII}—X_{2a} meets test 4 or test 5, precursor wherein the T_{BII} free valence is saturated with OZ or with Z or with $-Z^{I}-\underset{|}{N}-Z^{II}$, Z^{I} and Z^{II} being equal or different and having the Z values as above defined, depending on whether T_{BII} = CO or X, in connection with the tI and tII values;

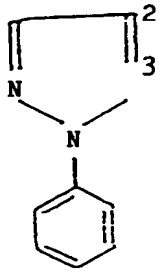
A = R—, has the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH_2 groups mentioned in the general formula, the following substituents can be present:

in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



in position 2: there may be Cl, Br;

in position 3: there may be CO, $-O-CH_2-CH_2-Cl$, OH;

in position 3-4: there may be a double bond;

in position 4-5: there may be a double bond;

in position 5-6: there may be a double bond;

in position 5-10: there may be a double bond;

in position 6: there may be Cl, F, CH_3, -CHO;

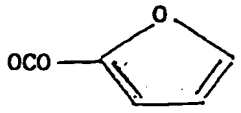
in position 7: there may be Cl, OH;

in position 9: thre may be Cl, F;

in position 11: there may be OH, CO, Cl, CH_3;

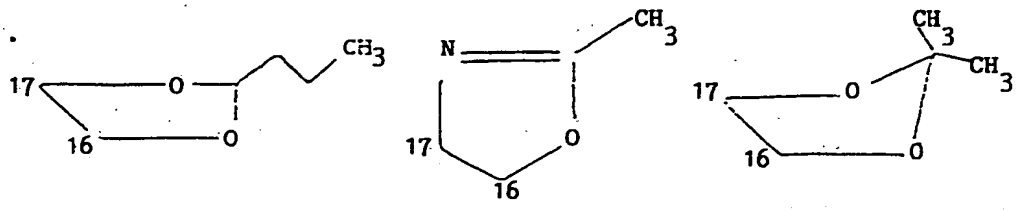
in position 16: there may be CH_3, OH, $=CH_2$:

in position 17: there may be OH, CH_3, $OCO(O)_{ua}(CH_2)_{va}CH_3$, C≡CH or



wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

in position 16-17: there may be the following groups:



R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms,

preferably R = R' = CH_3;

R" is $-(CO-L)_t-(L)_{t2}-(X_O^I)_{t1}-$

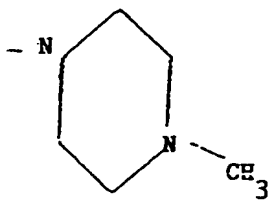
wherein t, t1 and t2 are integers equal to or different from each other, equal to 0 or 1, with the proviso that when t = 0 t2 = 1 and when t = 1 t2 = 0, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

the bivalent bridging group L is selected from:

$(CR_4R_5)_{na}(O)_{nb}(CR_4R_5)_{n'a}(CO)_{n'b}(O)_{n''b}(CO)_{n'''b}(CR_4R_5)_{n''a}$

wherein na, n'a, and n''a, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb, n'b, n''b and n'''b, equal to or different from each other, are integers equal to 0 or 1; R_4, R_5, equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3;

X_O^I is X as above defined, but R_{1c} is a linear or branched alkyl from 1 to 10 carbon atoms, or equal to X_2^I wherein X_2^I is equal to OH, CH_3, Cl, $N(-CH_2-CH_3)_2$, SCH_2F, SH, or



- wherein test 4 is the following: it is an analytical determination carried out by adding portions of methanol

solutions of the precursor of B or B_1 at a 10^{-4} M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the test solution; and then the inhibition induced by the precursor towards radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_S/A_C)X100$$

wherein A_S and A_C are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; the acceptance criterium of the compounds according to this test is the following: test 4 is met by B or B_1 precursor compounds if the inhibition percentage as above defined is higher than or equal to 50%;

wherein test 5 is the following: it is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B_1 or of C = $-T_C$-Y-H, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $Fe^{II}(NH_4)_2(SO_4)_2$; after having thermostatted the solution at 37°C for one hour, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M are

added, in the order, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B_1 or C = $-T_c-Y-H$ with respect to radical production by Fe^{II} is calculated as a percentage by means of the following formula:

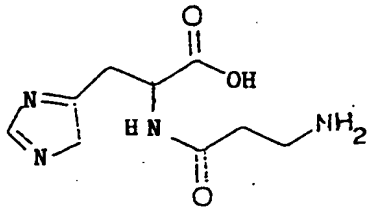
$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B_1 or C = $-T_c-Y-H$, having the free valence saturated as above indicated, is higher than or equal to 50%; provided that in the compounds of formula (I) are excluded the drugs with A = R-, wherein R is as above defined, when b_0 = 0 and C = $-T_c-Y_0-$ wherein the free valence of Y_0 is saturated as indicated above, s = 1 or 2.

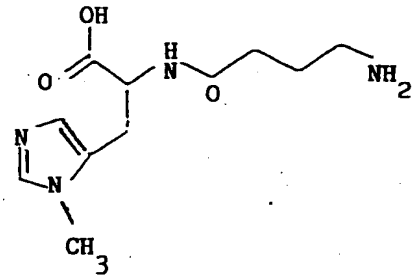
Preferably the B or B_1 precursor compound (precursor of the X_2 or X_{2a} radical in formulas (I) and (II) respectively) which meets test 4, is selected from the following classes of compounds:

- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl

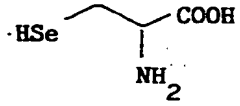
or isopropyl ester:



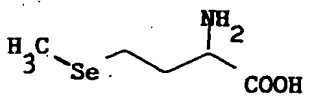
(CI)



(CII)



(CIII)



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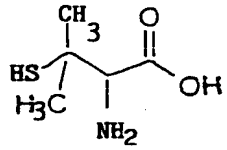
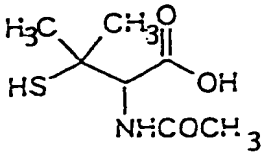


(CV)



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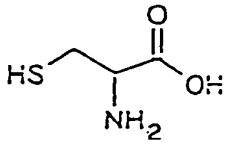

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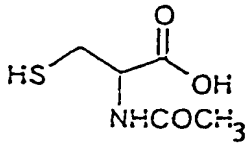
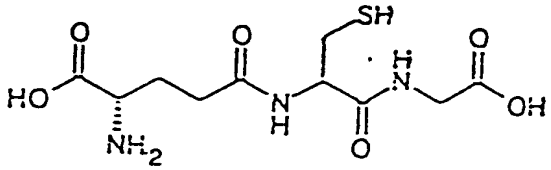


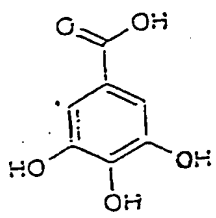
(CVIII)



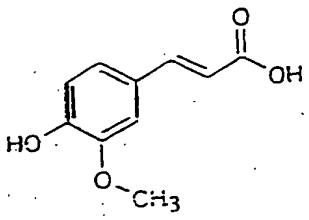
(CIX)

- hydroxyacids, selected from the following: gallic acid

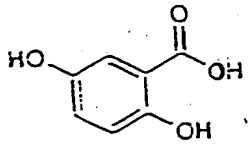
(formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydrocaffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



(DI)



(DII)



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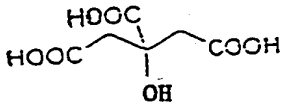
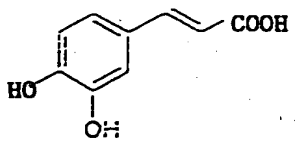


(DIV)



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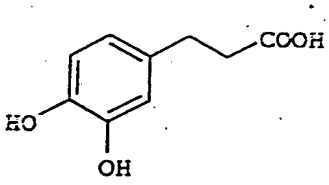

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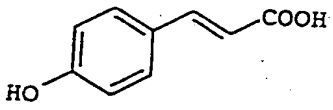

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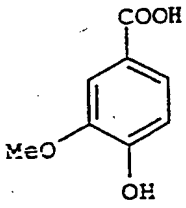

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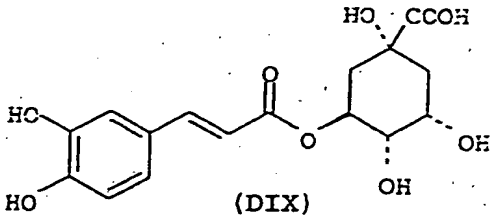

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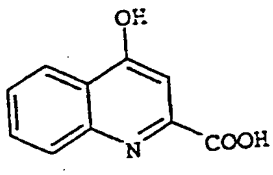

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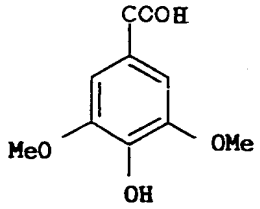
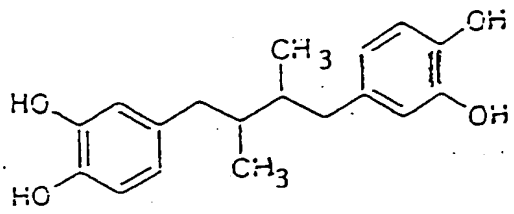
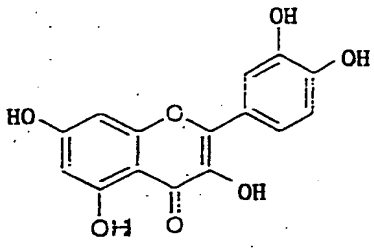


(DXI)

Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-tert-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-tert-butyl-p-hydroxytoluene (EXX), p-tert-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



(EI)



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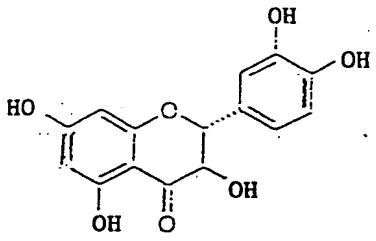

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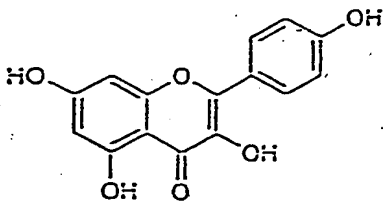

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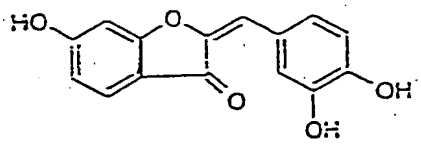

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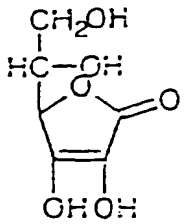

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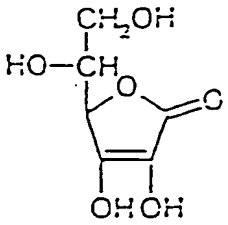

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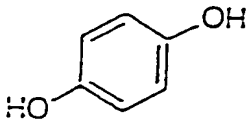

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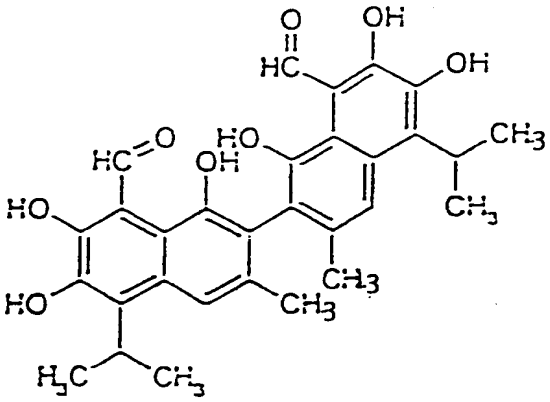

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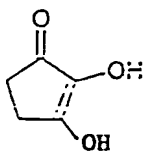

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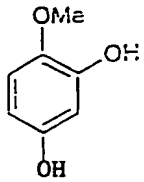

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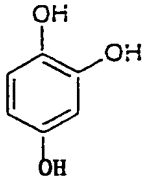

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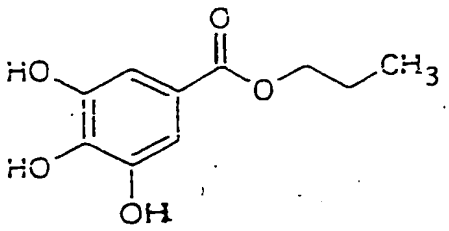

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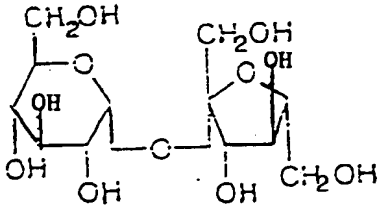

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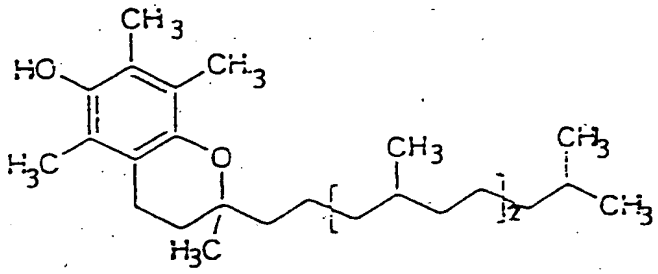

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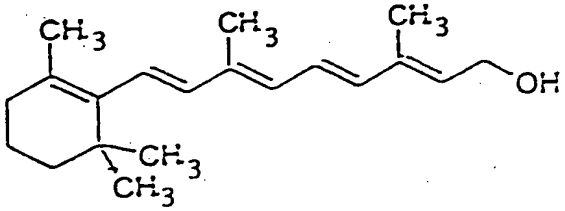

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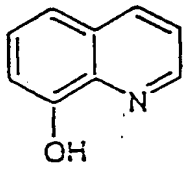

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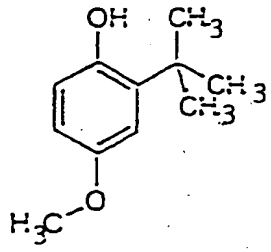

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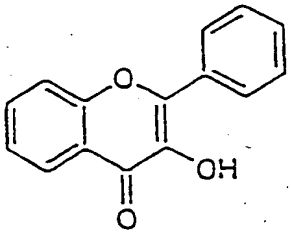

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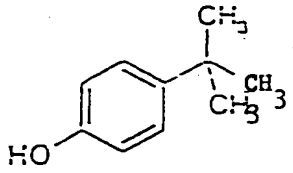

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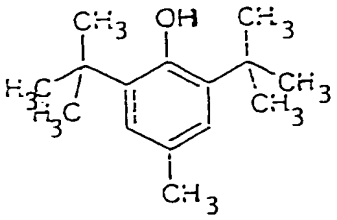

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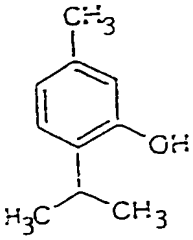

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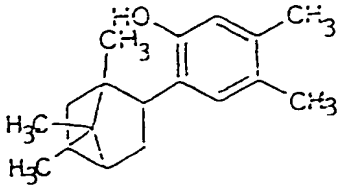

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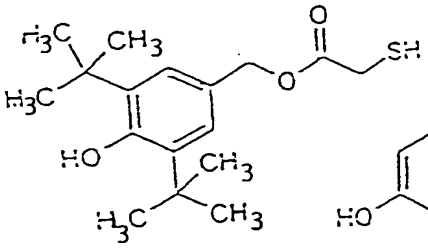
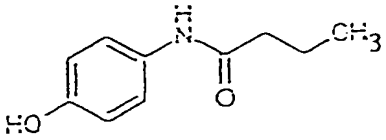
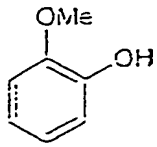


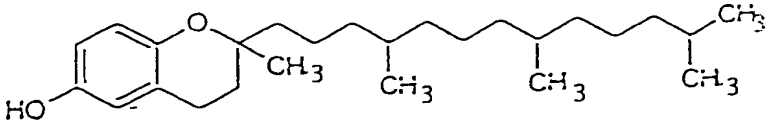
(EXXIV)



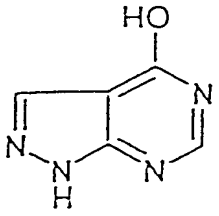
(EXXV)



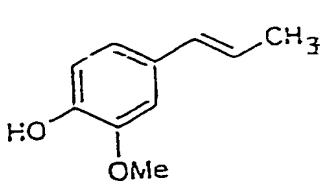
(EXXVI)



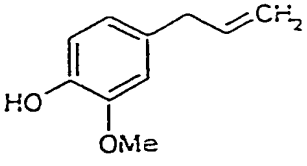
(EXXVII)



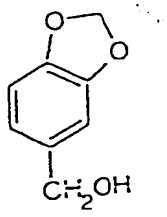
(EXXXI)



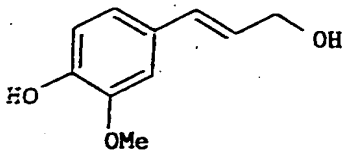
(EXXVIII)



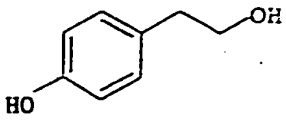
(EXXIX)



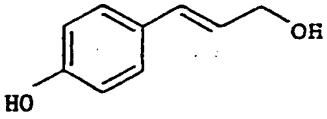
(EXXX)



(EXXXII)



(EXXXIII)



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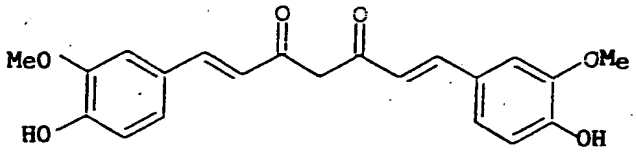
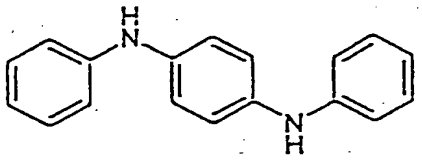
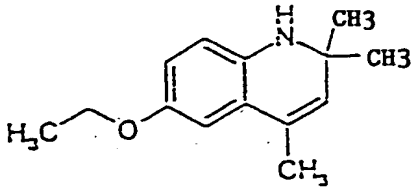


(EXXXV)

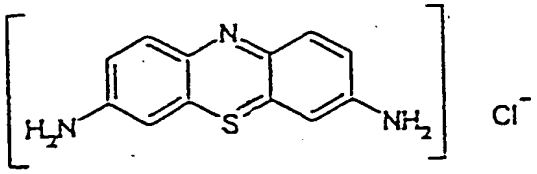
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (MIV):



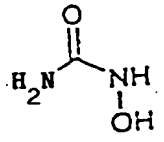
(MI)



(MII)

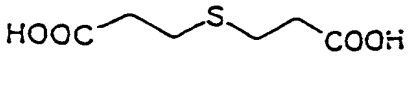


(MIII)

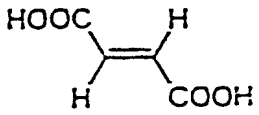


(MIV)

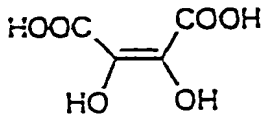
Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thioctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylendioxycinnamic acid (NVII), piperonylic acid (NVIII):



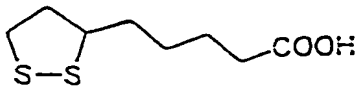
(NI)



(NII)



(NIII)



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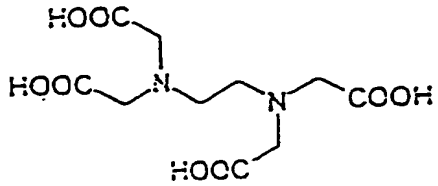
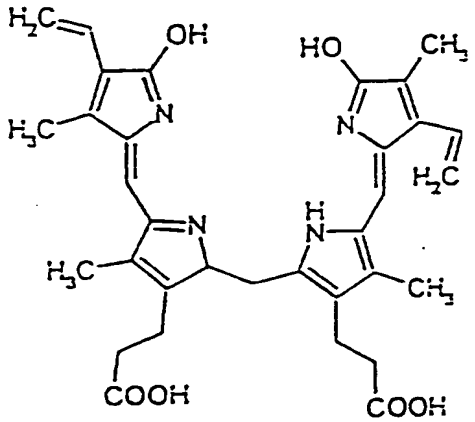
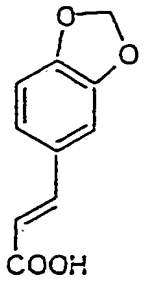


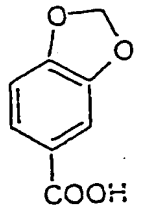
(NV)



(NVI)



(NVII)

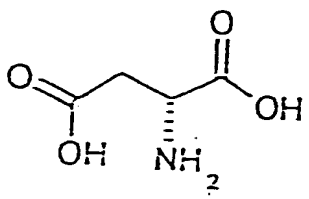


(NVIII)

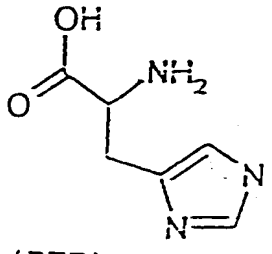
The above mentioned substances precursors of B or B_1 are prepared according to the known methods in the prior art, described, for example, in "The Merck Index, 12a Ed. (1996), herein incorporated by reference. When available, the corresponding isomers and optical isomers can be used.

Preferably the precursor compound of B or of B_1 (precursor of the X_2 or X_{2a} radical in formulas (I) and (II) respectively) which meets test 5, is selected from the following compounds:

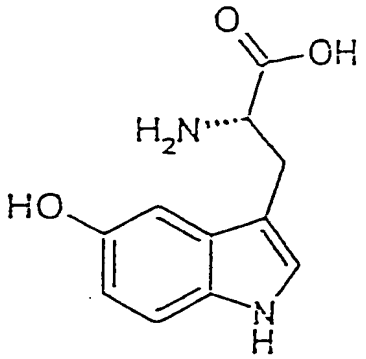
- Aminoacids: aspartic acid (PI), histidine (PII), 5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



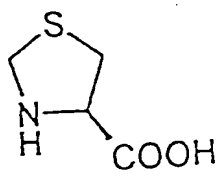
(PI)



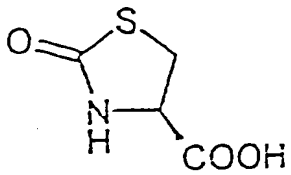
(PII)



(PIII)

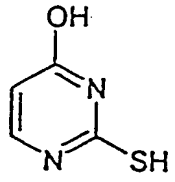


(PIV)



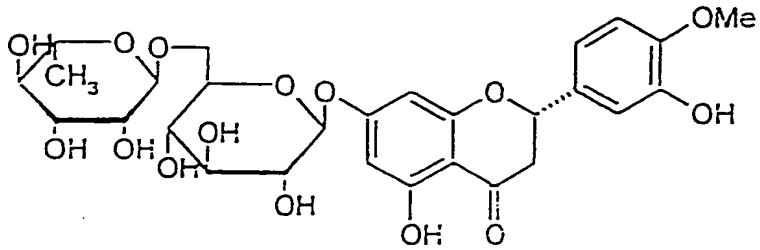
(PV)

mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1-α-OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1α-hydroxyvitamin D2 (QX) the compound derived from 1α,25-dihydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)

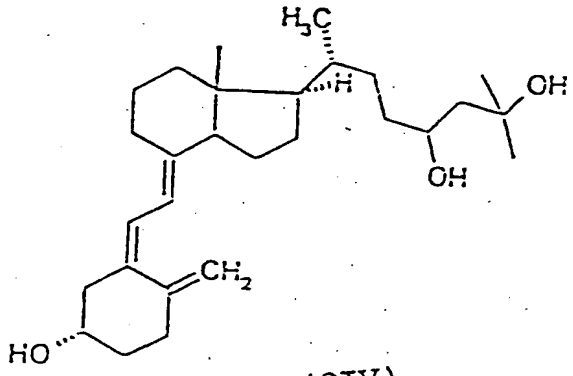


(QI)

(QII)



(QIII)



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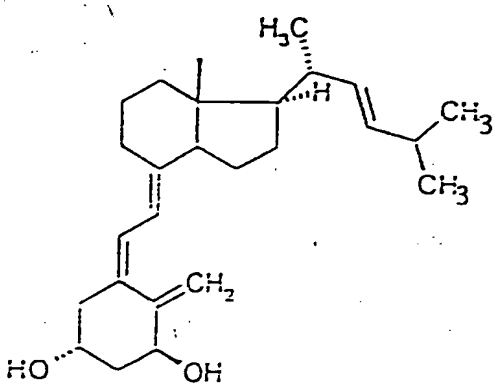
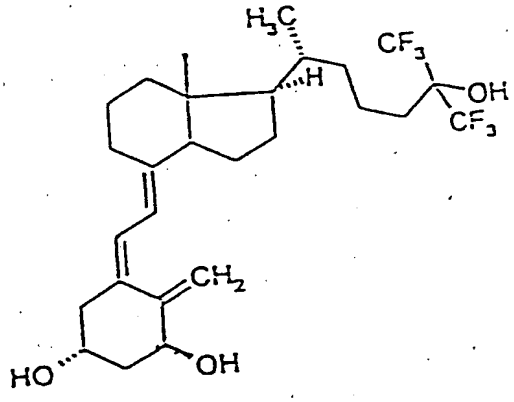
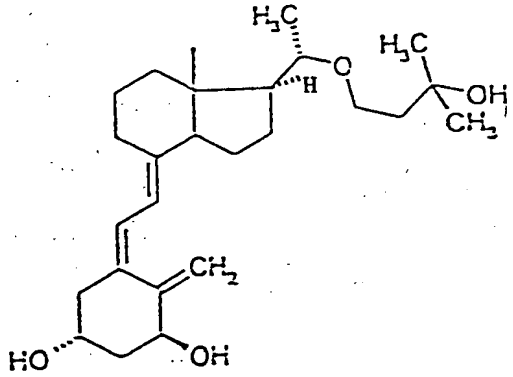


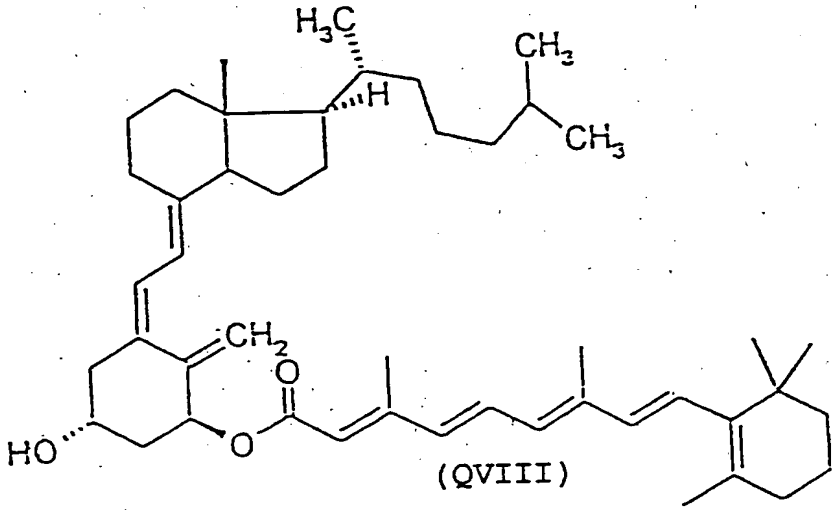
(QV)



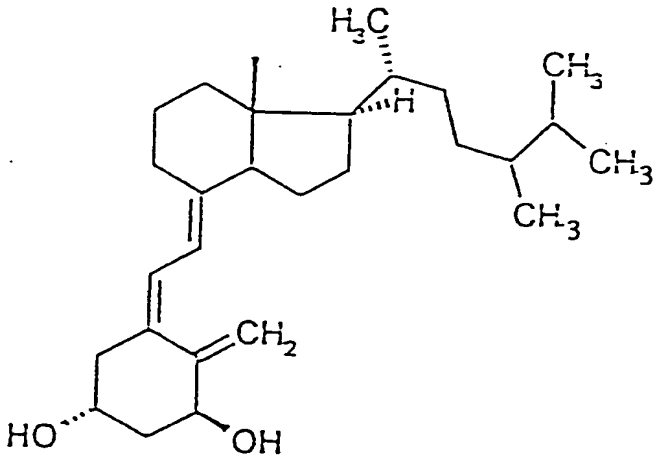
(QVI)



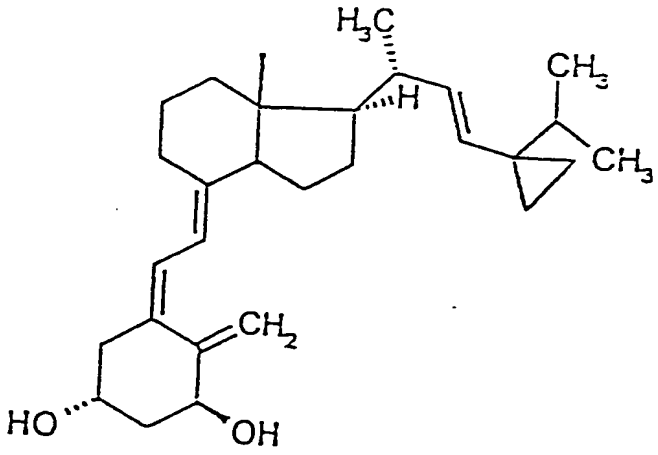
(QVII)



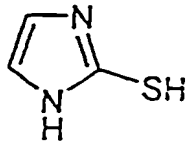
(QVIII)



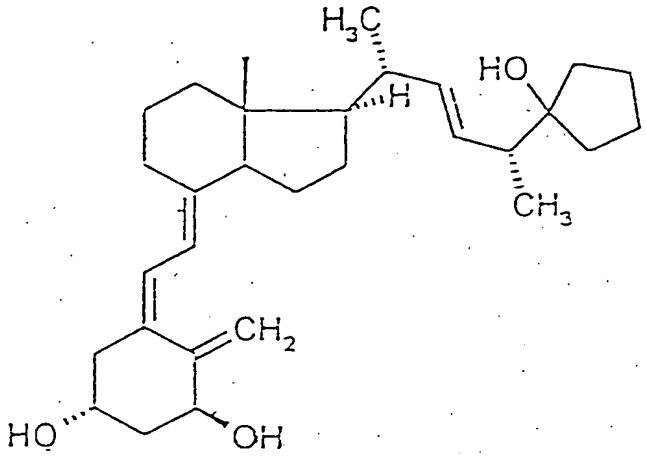
(QIX)



(QX)

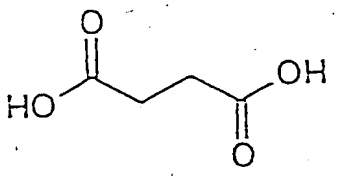


(QXII)



(QXI)

- succinic acid (RI)



(RI)

The precursor compounds of B or B_1 of the above mentioned groups P, Q and R are prepared according to the known methods in the prior art and described for example in "The Merck Index", 12[a] Ed. (1996), herein incorporated by reference.

The vitamin D3 derivative with retinoic acid (QVIII) is prepared as described in JP 93039261 (ref. C.A. 119 117617); the formula (QIX) compound according to EP 562497; 24,28-

methylene-1α-hydroxyvitamin D2 (QX) according to EP 578494; the derivative compound of dehydroxyvitamin D2 (QXI) according to EP 549,318.

The precursors of B or B_1 which meet test 4, are preferred.

The tests carried out to identify the precursors of B or B_1 are in detail the following:

Test 4 is a colorimetric test which affords to establish whether the precursors of B or B_1 inhibit the production of radicals from DPPH (2,2-diphenyl-1-picryl-hydrazyl) (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995). 100 μM solutions in methanol of the tested substances are prepared, and an aliquot of each of said solutions is added to a DPPH solution in methanol 0.1 M. After having stored the solutions at room temperature away from light for 30 minutes, their absorbances are read at the wave length of 517 nm, together with that of the corresponding DPPH solution at the same concentration. The absorbance decrease with respect to that of the solution of DPPH at the same concentration of the test solutions is determined. The effectiveness of the tested compound in inhibiting formation of radicals by DPPH is expressed by the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound together with DPPH and of

the solution containing only DPPH; the compounds precursor of B or B_1 meet test 4 when the inhibition percentage of radical production from DPPH, expressed as a percentage according to the above equation, is higher than or equal to 50% at the indicated concentration (10^{-4} M).

If the precursors of B or B_1 do not meet test 4, test 5 is carried out.

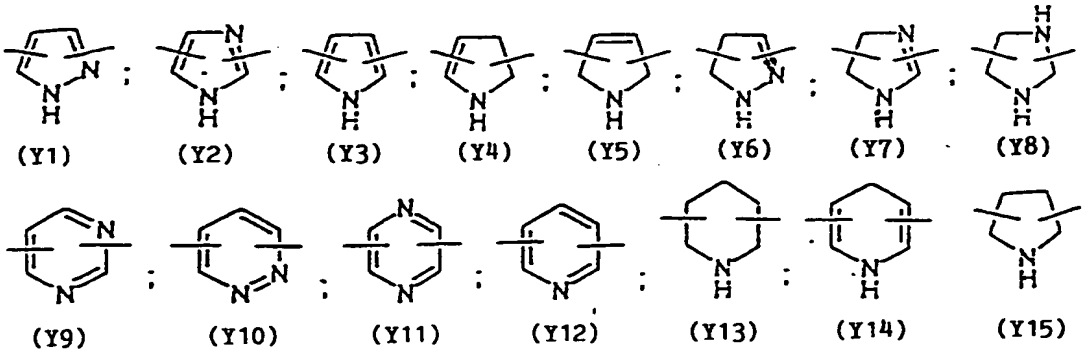
Test 5 is a colorimetric test wherein 0.1 ml aliquots of 10^{-4} M methanolic solutions of the tested products are added to test tubes containing a solution formed by 0.2 ml of 2 mM desoxyribose, 0.4 ml of phosphate buffer pH 7.4 100 mM and 0.1 ml of 1 mM $Fe^{--}(NH_4)_2(SO_4)_2$ in 2mM HCl. The test tubes are then maintained at 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in trichloroacetic acid water and 0.5 ml of an aqueous 0.1 M solution of thiobarbituric acid are added, in the order. A reference blank is formed by adding to a test tube containing only the above described aqueous solution of reactants 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration is developed the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances are read at 532 nm against the blank. The inhibition induced by the precursor of B or B_1 or C = $-T_c$-Y-H in comparison with the radical production by Fe^{II} is determined

by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage of radical production as above defined from the precursor of B or B_1 or C = $-T_c-Y-H$ is higher than or equal to 50%.

Y^3 in formula (III) is preferably selected from the following:



The most preferred of Y^3 is Y12 (pyridyl) substituted in positions 2 and 6. The bonds can find also in asymmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The compounds according to the present invention of formula (I) and (II) can be transformed into the corresponding salts. For example one way to form salts is the following: when in the molecule one nitrogen atom sufficiently basic to be salified, in organic solvent such as for example acetonitrile,

tetrahydrofuran, is present, it is reacted with an equimolecular amount of the corresponding organic or inorganic acid.

Preferably in the formula of the invention compounds Y or Y' of formula (III) is present.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examples of inorganic acids are: nitric, hydrochloric, sulphoric, phosphoric acids.

In the steroid precursors preferably R" = $-CO-CH_2OH$, $-CH(CH_3)-CH_2-CH_2-COOH$.

Among the steroid precursors those having the hydroxyl function in position 3 or in position 11, or having in R" an hydroxyl or carboxylic function in terminal position, are preferred.

The steroid precursors of A which can be mentioned and which are preferred, are those listed hereinunder, obtainable according to the processes known in the art.

As precursors and respective processes, those for example described in The Merck Index, ed. 12 of 1996, herein incorporated by reference, can be mentioned. The precursors (according to the Merck nomenclature) are the following, wherein H_2, H, R, R', R'' have the meaning mentioned in the compounds listed herein: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloro-

prednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

Unexpectedly the invention products of the formulas (I) and (II), in conditions of oxidative stress, have an improved therapeutic index compared with the precursor steroids.

For illustrative purposes the above mentioned tests are referred to the following compounds (see the tables attached to the description):

Test 4 (test for the precursor of B and B_1, ref. Table III)

N-acetylcysteine inhibits of 100% radical production from DPPH, therefore it meets test 4 and it can be used as precursor of B or B_1.

4-thiazolidincarboxylic acid does not inhibit radical production from DPPH, therefore it does not meet test 4: it can be used as precursor of B or B_1 if it meets test 5.

Test 5 (test for the precursor of B and B_1 or of C= $-T_c-Y-H$, ref. Table IV)

4-thiazolidincarboxylic acid meets test 5 since the inhibition is of 100%. Therefore the compound can be used as precursor of B or B_1 in formula (I).

The compounds of the invention can be used in the same therapeutic indications of the precursor drug with the above mentioned advantages.

The compounds of formula (I) or (II) are prepared by synthesis methods mentioned hereinunder.

The choice of the reactions for each method depends on the reactive group present in the steroid molecule, in the precursor compound of B or B_1, which can be, as above mentioned, bivalent or monovalent, and in the precursor compound of C.

The reactions are carried out with well known methods in the prior art, which allow to obtain bonds among the steroid, the precursor compound of B or B_1 and the precursor compound of

C as above defined.

When the reactive function of the steroid (for example -COOH, -OH) is involved in a covalent bond, for example of ester, amide, ether type, said function can be restored with the well known methods in the prior art.

Some synthesis schemes for obtaining the compounds of the invention are reported hereinafter:

A) Synthesis of the compounds of formula (I).

1. Synthesis of the compound obtained by reaction between the steroid and the compound precursor of B.

1a. When the steroid contains a carboxylic function (general formula: R-COOH) and the functional group of the precursor compound of B which binds itself to the carboxylic function has the formula XZ, X being as above defined and Z = H, the effected reactions depend on the nature of the second reactive group present in the precursor compound of B.

1a.1 When the second reactive group present in the precursor compound of B is a carboxylic group, the synthesis general scheme expects the initial formation of the acyl halide of the R-COHal steroid (Hal = Cl, Br) and the subsequent reaction with the HX group of the precursor compound of B:

$$RCOOH \dashrightarrow RCOHal + H\text{-}X\text{-}X_2\text{-}COOH \dashrightarrow R\text{-}T_B\text{-}X_2\text{-}COOH \qquad (IA.1)$$

X_2, T_B being as above defined.

When in the two reaction compounds other functional groups COOH and/or HX are present, they must be protected before the reaction according to the methods known in the prior art; for example as described in the publication by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The RCOHal acylhalide is prepared according to the known methods in the prior art, for example by thionyl or oxalyl chloride, P^{III} or P^{V} halides in inert solvents under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

Specifically, when the HX group of the precursor compound of B is NH_2, or OH or SH, the steroid of formula R-COOH is first converted into the corresponding acyl halide RCOHal, as above mentioned, and then reacted with the HX group of the precursor compound of B in the presence of an organic base, such as triethylamine, pyridine, etc. using an inert solvent in the reaction conditions such as toluene, tetrahydrofuran, etc. at a temperature in the range 0°C-25°C.

Alternatively to the previous synthesis, the steroid of formula R-COOH can be treated with an agent activating the carboxyl group selected from N,N'-carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide

in solvent such as for example DMF, THF, chloroform etc. at a temperature in the range -5°C - 50°C and the obtained commpound reacted in situ with the reactive function of the precursor compound of B for obtaining the compound of formula (IA.1).

1a.2 When the precursor compound of B contains two functional groups XZ, equal to or different from each other, X being as above defined and Z = H, the steroid having formula R-COOH is first treated with an agent activating the carboxyl group, as above described in 1a.1, and then with the precursor compound of B, after having protected one of the two reactive HX groups, for example with acetyl or tert-butyloxycarbonyl, restoring the initial function at the synthesis end. The scheme is the following:

$$RCOOH \xrightarrow{CDI,\ HX\text{-}X_2\text{-}X\text{-}G} R\text{-}T_B\text{-}X_2\text{-}X\text{-}G \longrightarrow R\text{-}T_B\text{-}X_2\text{-}XH \quad (IA.2)$$

wherein X, T_B, X_2 are as above defined and G is a protective group of the HX function.

2. Nitroxyderivative synthesis.

2a.1 When the compound obtained at the end of the previous step 1a. has formula (IA.1), the acid can be converted into the corresponding sodic salt and one can then follow the known prior art methods for preparing the final compound, for example according to one of the following synthesis schemes:

A.) $R\text{-}T_B\text{-}X_2\text{-}COONa + R_4\text{-}X_1\text{-}R_3 \dashrightarrow$

$R\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}R_3$ (1A.1b) $\xrightarrow{AgNO_3}$

$R\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}Y\text{-}NO_2$

wherein T_B, X_2, T_{BI}, T_C are as above defined, R_4 is selected from Cl, Br, Y is as above defined, X_1 is the Y radical free from the oxygen atom, R_3 is Cl, Br, Iodine, OH. If R_3 = OH the compound of formula (1A.1b) is subjected to halogenation, for example with PBr_3, PCl_5, $SOCl_2$, $PPh_3 + I_2$, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran. If R_3 is Cl, Br, Iodine, the compound of formula (1A.1b) is directly reacted with $AgNO_3$ as above mentioned.

B.) $R\text{-}T_B\text{-}X_2\text{-}COONa + Hal\text{-}Y\text{-}NO_2 \dashrightarrow$

$R\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}Y\text{-}NO_2$

C.)

$R\text{-}T_B\text{-}X_2\text{-}COCl + R_5\text{-}X_1\text{-}R_3 \rightarrow R\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}R_3$ (1A.1c)

$\xrightarrow{AgNO_3}$

$R\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-}R_3 \dashrightarrow R\text{-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}Y\text{-}NO_2$

wherein R_5 = OH or NHR_{1C}, R_{1C}, R_3 and the other symbols being as above defined.

When X_1 is a linear C_4 alkyl, the corresponding acid $R\text{-}T_B\text{-}X_2\text{-}COOH$ is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran obtaining the compound

(1A.1c) wherein R_3 = Br.

2a.2 When the compound obtained at the end of the previous step 1a. has formula (IA.2), the corresponding nitroxyderivative is obtained by treating an halogen-carboxylic acid of formula Hal-X_1-COOH, X_1 being as above defined, first with an agent activating the carboxyl group as described in 1A.1, and then with the compound of formula (IA.2), obtaining an halogen derivative, which is isolated and then dissolved in organic solvent, (ref. paragraph 2a.1), and treated with silver nitrate. The global reaction scheme is the following:

$$\text{Hal-}X_1\text{-COOH} \xrightarrow{\text{1) CDI, 2) R-}T_B\text{-}X_2\text{-XH}} \text{R-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-}X_1\text{-Hal} \xrightarrow{AgNO_3} \text{R-}T_B\text{-}X_2\text{-}T_{BI}\text{-}T_C\text{-Y-}NO_2$$

wherein T_B, X_2, T_{BI}, T_C, Y are as above defined.

Alternatively, the halide Hal-X_1-COCl can be used, wherein Hal is preferably bromine, which is let react with the compound of formula (IA.2).

1b. When the reactive function of the steroid is -OH (general formula: R-OH), the two functional groups present on the precursor compound of B can be the following:

1b.1 A carboxylic group, which reacts with the steroid OH function, and a HX group, the latter reactive group of the precursor compound of B being equal to or different from

the steroid functional group. The formula of the precursor compound of B is of the H-X-X_2-COOH type, wherein X and X_2 are as above defined.

The H-X- function of the precursor compound of B is protected according to the known prior art methods and the carboxyl is reacted, as above mentioned, according to the following scheme:

H-X-X_2-COOH -----→ G-X-X_2-COOH + R-XH ---→

R-T_B-X_2-X-G -----→ R-T_3-X_2-X-H (1B.1)

At the end of the reaction the HX function of the precursor compound of B is restored.

1b.2 When the precursor compound of B contains two carboxylic groups, it is treated with an equimolar amount of an agent activating the carboxyl group under the conditions previously described in 1a.1, and then reacted with the reactive OH function of the steroid molecule. Possible other reactive functions of HX type present in the two compounds must be carefully protected as previously mentioned. Lastly a compound of formula R-T_3-X_2-COOH (1B.2) is obtained.

2b. Nitroxyderivative synthesis.

2b.1 To obtain the final nitroxyderivative starting from the compound of formula R-T_B-X_2-X-H (1B.1), obtained at the end of the synthesis described in 1b.1, the (1B.1) compound is reacted with an halogenacid of formula Hal-X_1-

COOH which has been treated as previously described in paragraph 1a.1, or with the corresponding halogenacid chloride, the resulting compound is dissolved in organic solvent, for example acetonitrile or tetrahydrofuran and reacted with silver nitrate.

2b.2 To obtain the final nitroxyderivative starting from the compound of formula $R-T_3-X_2-COOH$ (1B.2), obtained at the end of the synthesis described in 1b.2, the acid is transformed into the corresponding sodic salt, it is reacted with a $R_4-X_1-R_3$ compound, previously defined in the reaction A. scheme of paragraph 2a.1, obtaining according to the same process therein mentioned the final nitroxyderivative. Alternatively, when X_1 is a linear C_4 alkyl, the acid (1B.2) is reacted with triphenyl-phosphine in the presence of an halogenating agent such as CBr_4 or N-bromosuccinimide in tetrahydrofuran and the resulting compound dissolved in organic solvent for example acetonitrile, tetrahydrofuran, is reacted with silver nitrate.

2b.3 Alternatively to the synthesis process according to 1b.1 and 2b.1, it is possible to react in a first step the HX-function of the precursor compound of B $HX-X_2-COOH$ with the acyl chloride of an halogenacid of formula $Hal-X_1-CO-Cl$, wherein Hal is preferably Br, and subsequently the carboxylic function of the so obtained compound, with the

steroid of formula R-OH. In the third and last step the -Hal group is substituted with $-ONO_2$ according to the process described in 2b.1. The reaction scheme is the following:

$$HX\text{-}X_2\text{-}COOH + Hal\text{-}X_1\text{-}COCl \longrightarrow Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}COOH$$

$$Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}COOH \quad (2B.3) \xrightarrow{R\text{-}XH} Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}T_B\text{-}R$$

$$Hal\text{-}X_1\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}T_B\text{-}R \xrightarrow{AgNO_3} O_2N\text{-}Y\text{-}T_C\text{-}T_{BI}\text{-}X_2\text{-}T_B\text{-}R$$

wherein T_C, T_{BI}, T_B, X_2, X_1, Y are as above defined.

In the previous scheme the nitration can alternatively be carried out on the acid compound of formula (2B.3).

In the above mentioned processes the steroid reaction with the precursor of B for the compounds of formula (I) is not carried out when $b_0 = 0$, and in the reaction with the precursor compound of C the steroid with its reactive function is directly used.

B) Synthesis of compounds of formula (II).

1a. When the steroid reactive function is a carboxylic group amd the precursor compound of B_1 contains only one functional reactive group of formula XH, X being as above defined, the steroid is initially converted into the corresponding acyl-halide (RCOCl), or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an halogen-acid compound, said function being equal to or different from that present on the precursor compound of B_1, said

halogen-acid having the formula:

$$\begin{array}{l} HX\text{-}X_1'\text{-}COOH \\ \quad | \\ \quad Hal \end{array} \qquad (IIA.1)$$

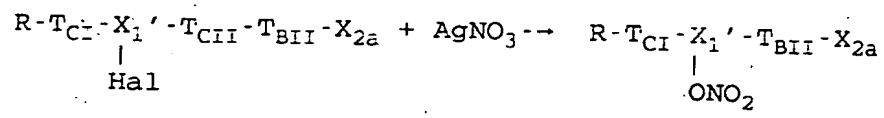
wherein X_1' is Y' as above defined without the oxygen atom through which the $-NO_2$ group is linked, X and Hal are as above defined.

The compound (IIA.1) can be obtained with the known method of the prior art.

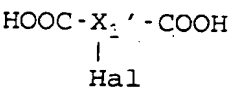
For example when X = NH, it can be obtained from the corresponding hydroxy-aminoacid, by protecting the aminic group by the corresponding tert-butyl-oxycarbonyl derivative and transforming the hydroxyl function into halogen group as described for the compound halogenation (1A.1b) in 2a.1.

The free carboxylic function of the compound resulting from the reaction with the steroid molecule is reacted with the function present in the molecule of the precursor of B_1, as previously illustrated in 1a.1 for the reaction between the steroid of formula R-COOH and the precursor compound of B. In the final step the halogen atom (Hal) present on the radical X_1 is substituted with an ONO_2 group by adding $AgNO_3$ to an organic solution of the compound. The reaction scheme is the following, exemplified starting from the RCOCl halide:

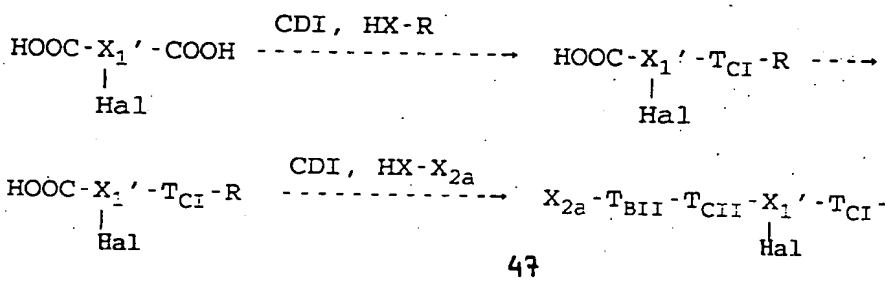
$$R\text{-}COCl + \begin{array}{l} HX\text{-}X_1'\text{-}COOH \\ \quad | \\ \quad Hal \end{array} \rightarrow \begin{array}{l} R\text{-}T_{CI}\text{-}X_1'\text{-}COOH \\ \quad | \\ \quad Hal \end{array} \quad (IIA.2) + HX\text{-}X_{2a} \rightarrow$$



1b. When the steroid reactive function is a OH group and the precursor compound of B_1 contains a reactive group of general formula XH, HX wherein X is as above defined, being equal to or different from OH, the synthesis is carried out starting from an halogendiacid compound of formula



X_1' being as above defined, said compound being prepared from the corresponding hydroxy-diacid as described for the halogenation of the compound (1A.1b) in 2a.1. The halogendiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the reactive function of the steroid molecule. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first, and reacted with the precursor compound of B_1 according to the following scheme:



The halogen atom is then substituted with the ONO_2 group as above mentioned.

3. Synthesis of the nitroso (s=1) derivatives of formula (I).

3a.1 The compound of formula (1A.1b) wherein R_3 = OH is reacted with sodium nitrite in a solvent formed of a mixture of water with tetrahydrofuran in the presence of hydrochloric acid. The reaction is widely illustrated in the prior art. The general scheme is the following:

$R\text{-}T_B\text{-}X_2\text{-}T_{B1}\text{-}T_C\text{-}X_1\text{-}OH + NaNO_2 \dashrightarrow A\text{-}B\text{-}C\text{-}NO$

3a.2 If the compound obtained at the end of step A has formula (IA.2) the corresponding nitroso derivative is obtained by treating an hydroxyacid of formula $HO\text{-}X_1\text{-}COOH$, X_1 being as above defined, first with an agent activating the carboxyl group, as described in 1a.1, then with 1A.2 and the resulting product with sodium nitrite as described in 3a.1.

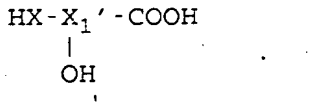
3b.1 To obtain the nitroso derivative starting from the compound of formula $R\text{-}T_B\text{-}X_2\text{-}XH$ (1B.1) obtained at the end of the synthesis described in 1b.1, the compound (1B.1) is reacted with an hydroxyacid as described in 3a.2.

3b.2 To obtain the nitroso derivative from the compound of formula $R\text{-}T_B\text{-}X_2\text{-}COOH$ (1B.2) obtained at the end of the synthesis described in 1b.2, the acid is transformed into the sodic salt and reacted with a compound $Hal\text{-}X_1\text{-}OH$, as

previously described, and the obtained alcohol is treated as described in 3a.1.

4) Synthesis of the nitroso derivatives of formula (II)

4a.1 When the steroid reactive function is a carboxylic group (general formula R-COOH) and the precursor compound of B_1 contains only one functional reactive group of formula XH, X being as above defined, R-COOH is initially converted into the corrsponding acyl-halide or treated with an agent activating the carboxyl group as described in 1a.1, and then reacted with the HX function of an hydroxy-acid compound, said function being equal to or different from that present on the precursor compound of B_1, said hydroxy-acid having the formula:



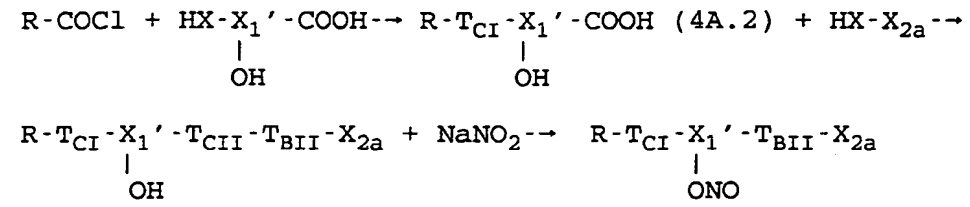
(4A.1)

wherein X_1' is Y' as above defined without the oxygen atom through which the -NO group is linked, X is as above defined.

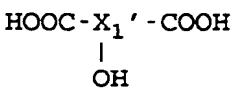
The free carboxylic function of the compound resulting from the reaction with the steroid molecule is reacted with the function present in the molecule of the precursor compound of B_1, as previously illustrated in 1a.1 for the reaction between the R-COOH acid and the precursor compound of B. In the final step the alcohol is transformed into the nitroso-derivative as described in

3a.1.

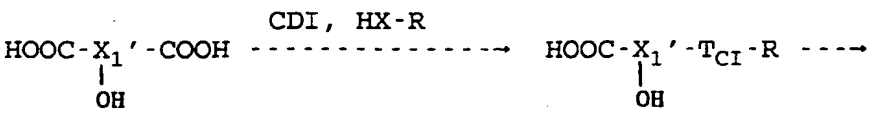
The reaction scheme is the following, exemplified starting from the RCOCl acid halide:

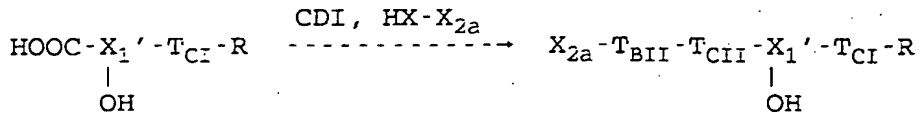


4b. When the reactive steroid function is a OH group and the precursor compound of B_1 contains a reactive group of general formula XH, HX in which X is as above defined being equal to or different from OH, the synthesis is carried out starting from an hydroxydiacid compound of formula



X_1' being as above defined, said hydroxydiacid compound is treated with an equimolar amount of an agent activating the carboxyl group, under the conditions previously described in 1a.1., and then it is reacted with the steroid reactive function. In the subsequent step the second carboxylic function is treated with an activating agent, as previously made for the first one, and reacted with the precursor compound of B_1 according to the following scheme:





The obtained compound is reacted as described in 3a.1.

The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topic use according to the well known methods in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

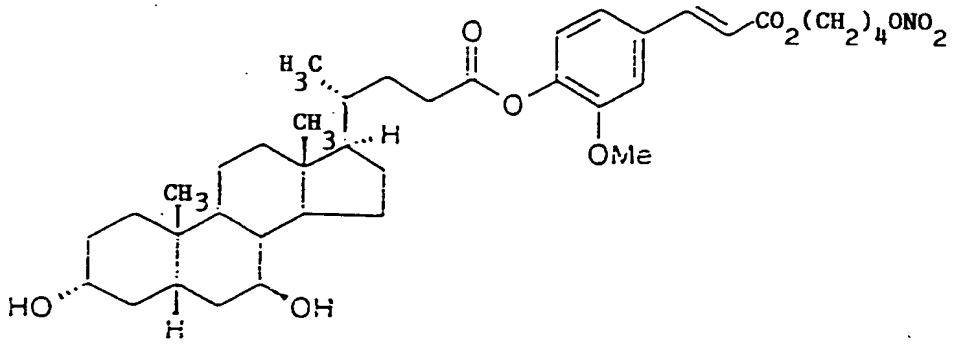
The amount on molar basis of the active principle in these formulations is the same, or lower, in comparison with that used of the corresponding precursor drug.

The daily administrable doses are those of precursor drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

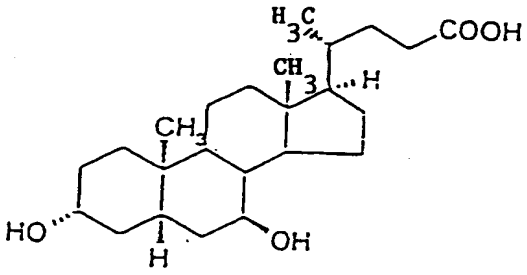
The following examples have the purpose to illustrate the invention and are not to be considered as limitative of the same.

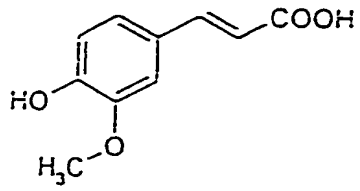
EXAMPLE 1

Preparation of 3-[4-[(3α,5β,7β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester



wherein the precursor steroid is ursodesoxycholic acid of formula (XL), the precursor of B is ferulic acid of formula (DII):





(XL) (DII)

a) synthesis of the 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester

To a solution of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid (10 g, 51.5 mmoles) in THF (400 ml) triphenylphosphine (2.7 g, 10.3 mmoles) and carbon tetrabromide (34.16 g, 10.3 mmoles) are added and the solution is left at room temperature,

under magnetic stirring, for 48 hours. The solid is filtered and then evaporated at reduced pressure. The obtained crude product is purified by chromatogrphy on silica gel eluting with n-hexane/ethyl acetate 7/3. 9 g of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester are obtained. M.p. = 86-89°C.

b) Synthesis of the 3-[4-[(3α,5β,7β)-3,7-dihydroxycolan-24-oiloxy] -3-methoxyphenyl]-2-propenoic acid 4-bromobutyl ester

To a solution of (3α,5β,7β)-3,7-dehydroxycolan-24-oic acid (2.9 g, 7.38 mmoles) dissolved in chloroform (25 ml) and dimethylacetamide (25 ml), 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid 4-bromobutyl ester (2.73 g, 8.28 mmoles) is added under stirring. To the solution cooled at 0°C, kept under stirring, N,N'-dicyclohexylcarbodiimide (2 g, 9.7 mmoles) and 4-dimethylamino pyridine (100 mg, 0.81 mmoles) are added. After 1 hour the mixture is heated to room temperature, after 24 hours the precipitate is filtered, the solvent is evaporated at reduced pressure. The residue is treated with ethyl acetate (150 ml) and washed with water (3X 100 ml). After the organic phase is anhydrified with sodium sulphate the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with n-hexane/ethyl acetate 1/9. 2.5 g of 3-[4-[(3α,5β,7β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl-2-propenoic acid 4-bromobutyl ester are obtained.

c) Synthesis of the 3-[4-[(3α,5β,7β)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester

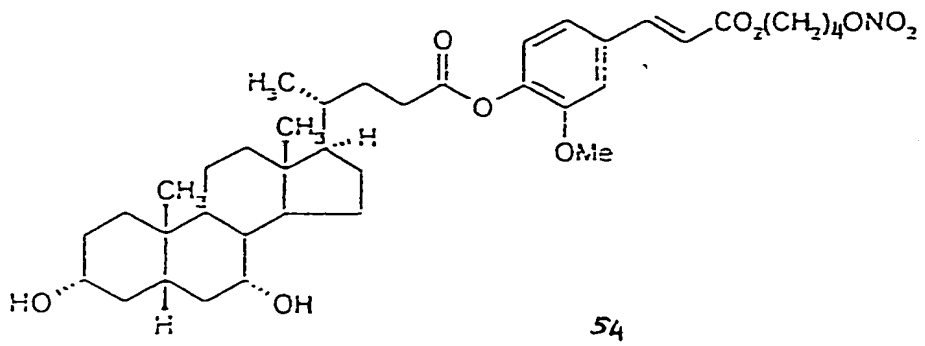
To a solution of 3-[4-[(3α,5β,7β)-3,7-dehydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-bromobutyl ester (2.3 g, 3.27 mmoles) in acetonitrile (20 ml) and tetrahydrofuran (5 ml) silver nitrate (0.84 g, 4.94 mmoles) is added under stirring and the mixture is heated to 80°C under magnetic stirring for 6 hours. When the reaction is over the precipitate is filtered and the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with methylene chloride/ethyl acetate 3/7. 1.5 g of 3-[4-[(3α,5β,7β)-3,7-dehydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propencic acid 4-nitroxybutyl ester are obtained. Total yield 32%.

Elementary analysis

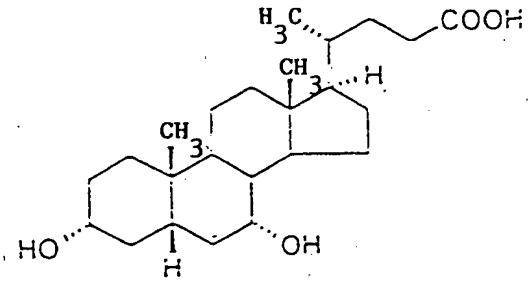
Calculated	C 66.55%	H 8.08%	N 2.04%
Found	C 66.59%	H 8.14%	N 1.99%

EXAMPLE 2

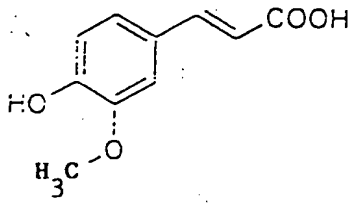
Preparation of 3-[4-[(3α,5β,7α)-3,7-dihydroxycolan-24-oiloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitroxybutyl ester



wherein the precursor steroid is chenodeoxycholic acid of formula (XLI) and the B precursor is ferulic acid of formula (DII)



(XLI)



(DII)

The compound is prepared following the procedure reported in Example 1. Total yield 28%.

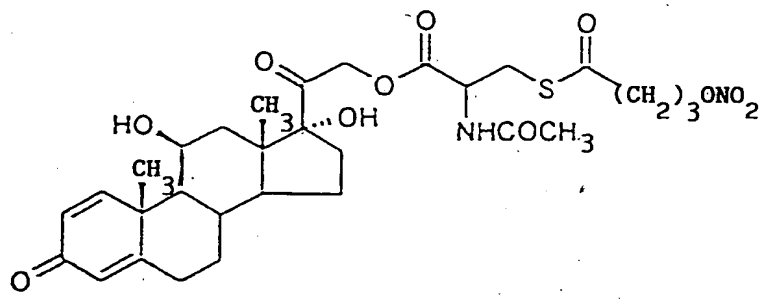
Elementary analysis

Calculated C 66.55% H 8.08% N 2.04%

Found C 66.64% H 8.13% N 1.94%

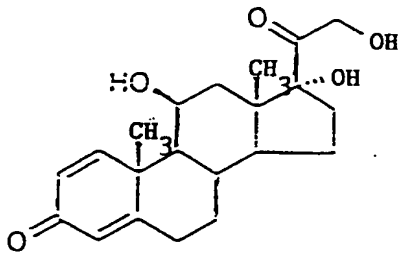
EXAMPLE 3

Preparation of (11β)-11,17-dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione

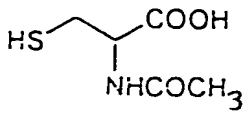


wherein the precursor steroid is prednisolone of formula (XLII)

and the precursor of B is N-acetyl cysteine of formula (CVIII)



(XLII)



(CVIII)

a) Synthesis of N-acetyl-S-(4-bromobutyroyl)cysteine

A solution of 4-bromobutyric acid (5.1 g, 30.6 mmoles) and 1,1'-carbonyldiimidazol (5.61 g, 34.6 mmoles)) in chloroform (50 ml) is left at room temperature under stirring for 1 hour. To the reaction mixture N-acetyl cysteine (5 g, 30.6 mmoles) dissolved in N,N-dimethylformamide (5 ml) and sodium ethylate (50 mg) is added under stirring. After 24 hours the solution is washed with HCl 1% and brine, the organic phase is anhydrified with sodium sulphate and evaporated at reduced pressure. The obtained crude product is purified by chromatography on silica gel column, eluting with ethyl acetate/chloroform 7/3. N-acetyl-S-(4-bromobutyroyl)cysteine is obtained.

b) Synthesis of (11β)-11,17-Dihydroxy-21[N-acetyl-S-(4-bromobutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione

To a solution of N-acetyl-S-(4-bromobutyroyl)cysteine (2.7 g, 8.64 mmoles) and (11β)-11,17,21-trihydroxypregn-1,4-diene-3,20-dione (3.2 g, 8.86 mmoles) in tetrahydrofuran (100

ml) cooled at 0°C and kept under stirring, N,N'-dicyclohexylcarbodiimide (1.9 g, 9.2 mmoles) and 4-dimethylaminopyridine (100 mg, 0.8 mmoles) are added. After 1 hour the mixture is heated to room temperature, after 24 hours the precipitate is filtered, the solvent is evaporated at reduced pressure. The residue is treated with ethyl acetate (150 ml) and washed with water (3X 100 ml). After having anhydrified the organic phase with sodium sulphate the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with chloroform/ethyl acetate 3/7. 0.94 g of (11β)-11,17-dehydroxy-21[N-acetyl-S-(4-bromobutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione are obtained.

c) Synthesis of (11β)-11,17-Dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione

To a solution of (11β)-11,17-dehydroxy-21[N-acetyl-S-(4-bromobutyroyl)cysteinyloxy]-pregn-1,4-diene-3,20-dione (0.8 g, 1.28 mmoles) in acetonitrile (10 ml) and tetrahydrofuran (5 ml) silver nitrate (0.4 g, 2.35 mmoli) is added under stirring and the mixture is heated to 80°C under magnetic stirring for 20 hours. At the end of the reaction the precipitate is filtered and the solvent is evaporated. The obtained crude product is purified by chromatography on silica gel column eluting with methylene chloride/ethylacetate 3/7. (11β)-11,17-dehydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-1,4-diene-

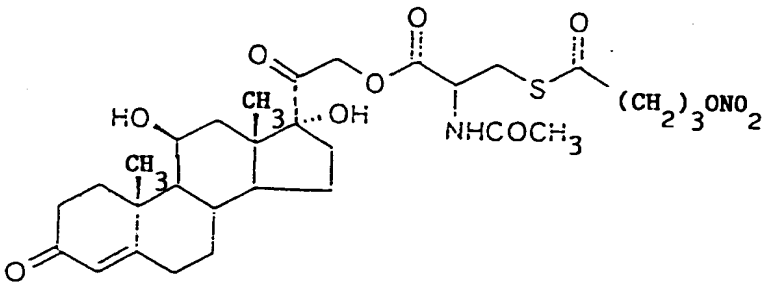
3,20-dione is obtained. Total yield 12%.

Elementary analysis

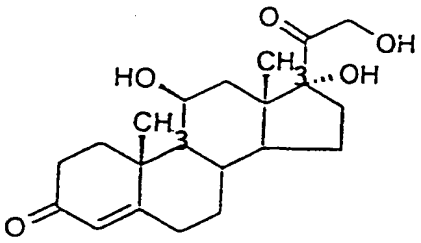
Calculated	C 56.59%	H 6.33%	N 4.40%	S 5.04%
Found	C 56.63%	H 6.38%	N 4.36%	S 5.01%

EXAMPLE 4

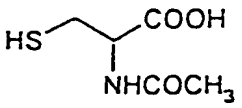
Preparation of (11β)-11,17-Dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-pregn-4-ene-3,20-dione



wherein the precursor steroid is hydrocortisone of formula (XLIII) and the precursor of B is N-acetyl cysteine of formula (CVIII)



(XLIII)



(CVIII)

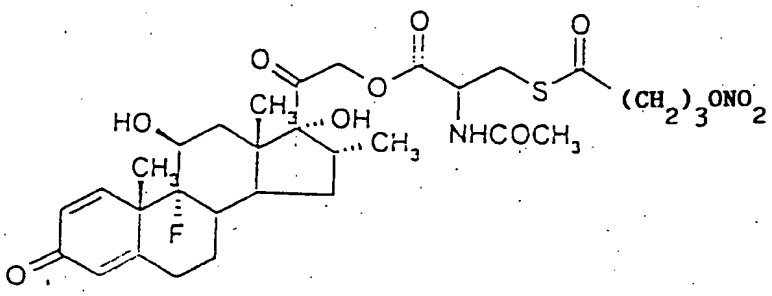
The compound is prepared according to the procedure reported in Example 3. Total yield 15%.

Elementary analysis

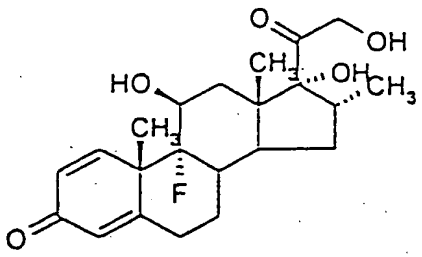
Calculated	C 56.37%	H 6.78%	N 4.39%	S 5.02%
Found	C 56.39%	H 6.81%	N 4.31%	S 4.93%

EXAMPLE 5

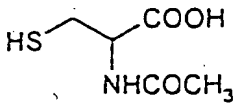
Preparation of (11β,16α)-9-Fluoro-11,17-dihydroxy-21[N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy]-16-methylpregn-1,4-diene-3,20-dione



wherein the precursor steroid is desamethasone of formula (X-LIV) and the precursor of B is N-acetyl cysteine of formula (CVIII)



(XLIV)



(CVIII)

The compound is prepared according to the procedure reported in Example 3. Total yield 17%.

Elementary analysis

Calculated	C 55.68%	H 6.18%	N 4.19%	S 4.79%

Found C 55.72% H 6.22% N 4.15% S 4.75%

PHARMACOLOGICAL TESTS

EXAMPLE

Acute Toxicity

Acute toxicity has been evaluated by administering to a group of 10 rats weighing 20 g a single dose of each of the tested compounds, by cannula, by os in an aqueous suspension of carboxymethylcellulose 2% w/v.

The animals are kept under observation for 14 days. In no animal of the group toxic symptoms appeared even after a 100 mg/Kg dose administration.

EXAMPLE F1

Experimental in vivo model with N^{w}-nitro-L-arginine-methyl ester (L-NAME): effect of the precursor steroids and of the corresponding compounds according to the present invention on the endothelial dysfunction induced by L-NAME.

The experimental model adopted is according to J. Clin. Investigation 90, 278-281,1992.

The endothelial dysfunction is evaluated by determining the damage the hepatic damage (GPT increase), and the vascular endothelium or cardiovascular damage (blood hypertension) induced by L-NAME administration.

The animals (Long Evans rats, average weight 350-450 g) are divided in groups as herein below described. The group receiving L-NAME is treated for 4 weeks with said compound

dissolved at the concentration of 400 mg/litre in drinking water. The following groups (No. 10 animals for group) are constituted:

A) Control groups:

1° group: treatment: only carrier (physiologic solution),

2° group: treatment: carrier + L-NAME,

B) Groups treated with the drug:

3° group: treatment: carrier + drug,

4° group: treatment: carrier + drug + L-NAME.

The drugs screened in the test are hydrocortisone, desamethasone, prednisolone, chenodeoxycholic acid, ursodesoxycholic acid and the corresponding derivatives according to the present invention.

In those groups of rats treated, respectively, with hydrocortisone, desamethasone, prednisolone and thereof corresponding compounds according to the present invention, the blood-pressure is determined.

In those groups of rats treated, respectively, with ursodesoxycholic acid and chenodeoxycholic acid and thereof corresponding compounds according to the present invention, GPT is determined.

Each drug is administered by intraperitoneal route once a day for 4 weeks.

At the end of the four weeks access to water is prevented and after 24 hours the animals are sacrificed.

Four hours after the last administration the blood-pressure is determined.

Damage to the vascular endothelium is determined, as said by the cardiovascular effects induced by L-NAME (increase of the blood pressure). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

Results are reported in Tables I and II. The % blood-pressure and GPT values are referred to the corresponding value found in the animals of the 1st control group. The average value of the blood pressure in this group was of 105 mmHg.

The results obtained show that the steroidal precursors cause hepatic damage (ursodesoxycholic acid and chenodeoxycholic acid) and arterial hypertension (hydrocortisone, desamethasone, prednisolone). GPT and blood pressure values of the treated rats are higher compared both with the corresponding groups treated with drug in the absence of L-NAME and with the controls treated with L-NAME. The products of the invention are instead better tolerated in comparison with the corresponding precursors, even in animals not pretreated with L-NAME.

EXAMPLE F2

Test 4: inhibition of the radical production from DPPH of some substances used to prepare the precursors of B or B1

The method is based on a colorimetric test in which DPPH

(2,2-diphenyl-1-picryl-hydrazyl) is used as the compound-forming radicals (M.S. Nenseter et Al., Atheroscler. Thromb. 15, 1338-1344, 1995).

Solutions in methanol of the tested substances at a final concentration 100 µM are initially prepared. 0.1 ml of each of these solutions are added to aliquots of 1 ml of a methanol solution 0.1 M of DPPH and then the final volume is brought to 1.5 ml. After having stored the solutions at room temperature away from light for 30 minutes, the absorbance at the wave length of 517 nm is read. It is determined the absorbance decrease with respect to the absorbance of a solution containing the same concentration of DPPH.

The efficacy of the test compound to inhibit the production of radicals, otherwise said antiradical activity, is expressed by the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are, respectively, the absorbance values of the solution containing the test compound together + DPPH and of the solution containing only DPPH.

The compound to be used as precursor of B or B_1 according to the present invention meets test 4 if it inhibits radical production from DPPH in a percent equal to or higher than 50%.

In Table III are reported the results obtained in said test with the following compounds: N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid, 4-thiazolidin

carboxylic acid and 2-oxo-4-thiazolidincarboxylic acid.

Table III shows the following:

- N-acetylcysteine, cysteine, ferulic acid, (L)-carnosine, gentisic acid meet test 4 since they inhibit the production of radicals induced by DPPH to an extent higher than 50%. Therefore they can be used as precursors of the B compound in the synthesis of the compounds according to the present invention.

- 4-thiazolidin carboxylic acid and the 2-oxo-4-thiazolidin carboxylic acid do not meet test 4 since they do not inhibit radical production from DPPH. Therefore they can be used as precursors of B or B_1 if they meet test 5.

EXAMPLE F3

Test 5: Inhibition of the radical production from Fe^{II} from compounds used as precursors of B, B_1 or C = $-T_c-Y-H$.

0.1 ml aliquots of 10^{-4} M methanolic solutions of 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid are added to test tubes containing an aqueous solution formed by mixing 0.2 ml of 2 mM desoxyribose, 0.4 ml of buffer phosphate pH 7.4 100 mM and 0.1 ml of 1 mM $Fe^{II}(NH_4)_2(SO_4)_2$ in 2mM HCl. The test tubes are then kept at a temperature of 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in trichloroacetic acid in water and 0.5 ml of an aqueous solution 0.1 M thiobarbituric acid are added in the order. A reference blank is constituted by substituting the above 0.1 ml

aliquots of the test compound methanolic solutions with 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration develops the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances at 532 nm are read against the blank.

The inhibition induced by the precursor of B or B_1 or C = $-T_c-Y-H$ (wherein the free valence is saturated as above defined) with respect to radical production from Fe^{II} is determined as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt.

The results are reported in Table IV, which shows that both acids meet test 5 since they inhibit radical production from Fe^{II} in a percentage higher than 50%. Therefore both 4-thiazolidin carboxylic acid and 2-oxo-4-thiazolidin carboxylic acid can be used as precursors of B, B_1 or C = $-T_c-Y-H$ for obtaining compounds of the present invention.

EXAMPLE F4

Example F1 was repeated with three groups of rats (each group of of ten animals), one control group not receiving L-NAME and two groups receiving L-NAME, and i.p. administered as it

follows :

a. control group (not receiving L-NAME) : the carrier (physiologic solution),

b. 1st group receiving L-NAME (group b - comparative) administered at the same time with 25 mg/Kg (0.064 mmoles/Kg) of dexamethasone + 10.4 mg/Kg (0.064 mmoles/Kg) of N-acetylcysteine in the same above carrier,

c. 2nd group receiving L-NAME (group c) administered with 42.5 mg/Kg (0.064 mmoles/Kg) of the dexamethasone derivative according to the invention (ref. ex. 5) in the same above carrier.

In this experiment vascular tolerability, i.e. the rise in blood pressure (vascular damage) was determined in the animals of groups b and c and expressed as percentages to that of the control group a, assumed to be 100 %.

The results are reported in Table V and show that the mixture administered to group b (comparative) induced in the animals an higher blood pressure increase than the compound of the invention (group c).

EXAMPLE F5

Example F1 was repeated with three groups of rats (each group of of ten animals), one control group not receiving L-NAME and two groups receiving L-NAME, and i.p. administered as it follows :

a. control group (not receiving L-NAME) : the carrier

(physiolcgic solution),

b. 1st group receiving L-NAME (group d - comparative) administered at the same time with 100 mg/Kg (0.25 mmoles/Kg) of ursodesoxycholic acid + 49.5 mg/Kg (0.25 mmoles/Kg) of ferulic acid in the same above carrier,

c. 2nd group receiving L-NAME (group e) administered with 175 mg/Kg (0.25 mmoles/Kg) of the ursodesoxycholic derivative according to the invention (ref. ex. 1) in the same above carrier.

In this experiment hepatic tolerability, i.e. the rise in GPT (hepatic damage) was determined in the animals of groups d and e and expressed as percentages to that of the control group a, assumed to be 100 %.

The results are reported in Table VI and show that the mixture administered to group d (comparative), induced in the animals an higher GPT increase than the compound of the invention (group e).

Table I

Study of vascular tolerability of hydrocortisone, dexamethasone and prednisolone, and of the corresponding derivatives according to the invention, in animals (rats) both not treated and treated with L-NAME. Vascular tolerability is indicated as % variation of the blood pressure (hypertension) with respect to the controls not treated with L-NAME and treated with the only carrier (physiological solution)

Compound	Animals non treated with L-NAME		Animals treated with L-NAME	
	dose mg/Kg i.p.	Blood pressure variation %	dose mg/Kg i.p.	Blood pressure variation %
carrier	-	100	-	140
hydrocortisone	10	115	5	160
hydrocortisone der. Ex. 4	10	98	5	120
dexamethasone	5	125	25	170
dexamethasone der. Ex. 5	5	103	25	125
prednisolone	10	119	15	165
prednisolone der. Ex. 3	10	102	15	110

Table II

Study of hepatic damage, determined by GPT assay, of chenodeoxycholic acid and ursodesoxycholic acid, and of the corresponding derivatives according to the invention, in animals (rats) both not treated and treated with L-NAME. The % variation of GPT with respect to the controls not treated with L-NAME and treated with the only carrier (physiological solution)

Compound	animals non treated with L-NAME		Animals treated with L-NAME	
	dose mg/Kg i.p.	GPT var. %	dose mg/Kg i.p.	GPT var. %
carrier	-	100	-	230
chenodeoxycholic acid	100	150	100	350
chenodeoxycholic acid der. Ex. 2	100	105	100	130
ursodesoxycholic acid	100	130	100	276
ursodesoxycholic acid der. Ex. 1	100	103	100	123

Table III

Test 4: Screening of the effectiveness of some substances to inhibit radical production from DPPH.	
Compound	% inhibition radical production from DPPH
Solvent	0
N-acetylcysteine	100
Cysteine	100
Ferulic acid	100
(L)-carnosine	80
Gentisic acid	80
2-oxo-4-thiazolidin carboxylic acid	0
4-thiazolidin carboxylic acid	0

Table IV

Test 5 : study on the effectiveness of the listed substances to inhibit radical production induced by Fe^{II}	
Compound	% Radical Inhibition from Fe^{II}
White	0
2-oxo-4-thiazolidin carboxylic acid	100
4-thiazolidin carboxylic acid	100

Table V

Study of vascular tolerability in animals (rats) treated with L-NAME and i.p. administered with a mixture of dexamethasone + N-acetylcysteine and with the derivative of dexamethasone of ex. 5 according to the invention. Vascular tolerability is indicated as % variation of the blood pressure (hypertension) with respect to the controls not treated with L-NAME and treated with the only carrier.

Compound	dose mg/Kg i.p.	Blood pressure variation %
controls	-	100
group b - comparative dexamethasone (A)+ N-acetyl cysteine (B)	25(A)+10.4(B)	170
group c dexamethasone der. Ex. 5	42.5	125

Table VI

Study of hepatic tolerability in animals (rats) treated with L-NAME and i.p. administered with a mixture of ursodesoxycholic acid + ferulic acid and with the derivative of ursodesoxycholic acid of ex. 1 according to the invention. Hepatic damage is indicated as % variation of GPT with respect to the controls not treated with L-NAME and treated with the only carrier.

Compound	dose mg/Kg i.p.	GPT variation %
controls	-	100
group d - comparative ursodesoxycholic acid (C)+ ferulic acid (D)	100(C)+49.5(D)	180
group e ursodesoxycholic acid der. ex. 1	175	123

CLAIMS

1. Steroidal compounds or their salts having the following general formulas (I) and (II):

$$A—(B)_{b0}—C\text{-}N(O)_s \qquad (I)$$

wherein:

s = is an integer equal to 1 or 2, preferably s = 2;

b0 = 0 or 1;

A = R—, wherein R is the steroidal drug radical as defined hereunder,

B = $-T_B—X_2—T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when the reactive function in the precursor steroid is -OH; T_B = X when the reactive function in the precursor steroid is -COOH;

X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl having from 1 to 5 crbon atoms, or a free valence;

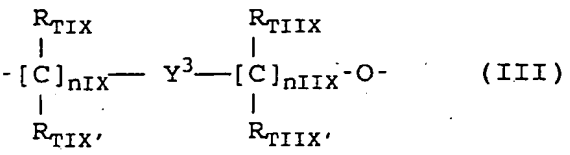
T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0, tx = 0 when txx = 1; X is as above defined;

X_2 is a bivalent bridging group as defined hereunder;

C is the bivalent radical $-T_C-Y-$ wherein

T_C = (CO) when tx = 0, T_C = X when txx = 0, X being as above defined;

Y is:



(III)

wherein:

nIX is an integer between 0 and 3, preferably 1;

nIIX is an integer between 1 and 3, preferably 1;

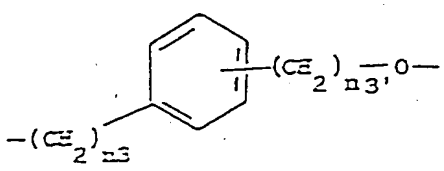
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen atom, said ring having 5 or 6 atoms,

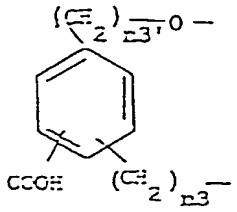
or Y is Y_0, selected from the following:

- an alkylenoxy group R'O wherein R' is linear or when possible branched C_1-C_{20}, preferably having from 1 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above defined; or

-



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



wherein n3 and n3' have the above mentioned meaning

- $(CH_2\text{-}\underset{\underset{ONO_2}{|}}{CH}\text{-}CH_2\text{-}O)_{nf'}$-

- -$(CH_2\text{-}\underset{\underset{ONO_2}{|}}{CH}\text{-}CH_2\text{-}O)_{nf'}$-

wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- -$(\underset{\underset{R_{1f}}{|}}{CH}\text{-}CH_2\text{-}O)_{nf}$-

- -$(CH_2\text{-}\underset{\underset{R_{1f}}{|}}{CH}\text{-}O)_{nf}$-

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4;

preferably Y = $-Y_0$ = R'O- wherein R' is as above defined; preferably R' is a C_1-C_6 alkyl;

$$A\text{—}C_1\text{—}B_1 \qquad \text{(II)}$$
$$\quad\;\; |$$
$$\quad N(O)_s$$

wherein:

C_1 = $-T_{CI}-Y'(-T_{CII}-$

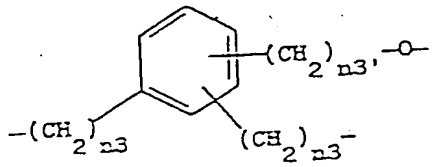
wherein T_{CI} and T_{CII} are equal or different,

T_{CI}= (CO) when the reactive function of the precursor steroid is -OH, T_{CI} = X when the reactive function of the precursor steroid is -COOH, X being as above defined;

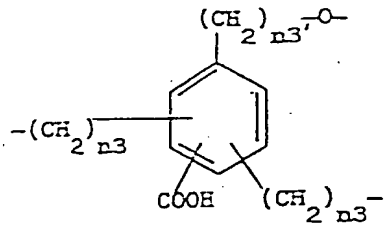
T_{CII}= $(CO)_{tI}$ or $(X)_{tII}$, wherein tI and tII have the 0 or 1 value; with the proviso that tI = 1 when tII = 0; tI = 0 when tII = 1; X is as above defined;

Y' is as Y above defined, but with three free valences instead of two, preferably selected from the following:

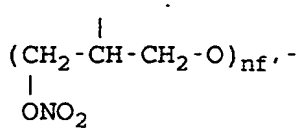
- a $-R'(O-$ group wherein R' is C_1-$_{20}$ linear or branched, preferably having from 1 to 6 carbon atoms, or a saturated ring having from 5 to 7 carbon atoms, optionally substituted; or



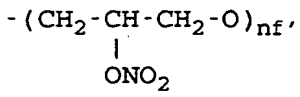
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



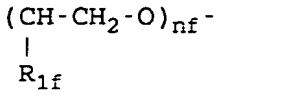
wherein n3 and n3' have the above mentioned meaning;



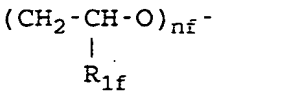
wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein nf' is an integer from 1 to 6 preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;



wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 1 to 4; wherein one hydrogen atom on one of the carbon atoms is substituted by a free valence;

preferably Y' = - R'O- wherein R' is a linear or branched C_2-C_4, the oxygen which in Y' is covalently linked to the $-N(O)_s$ group finds at the end of the free bond indicated in C_1 formula;

or Y' = Y_0 as defined in (I) but with three free

valences instead of 2;

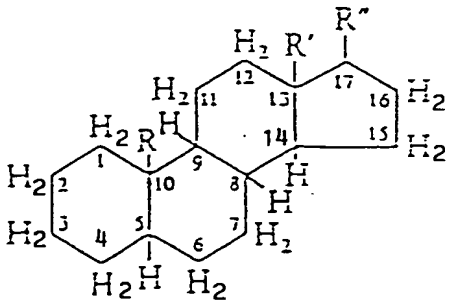
B_1 = $-T_{BII}—X_{2a}$

wherein X_{2a} is a monovalent radical,

T_{BII} = (CO) when tI = 0, T_{BII} = X when tII = 0, X being as above defined;

- X_2, bivalent radical is such that the corresponding B precursor: $-T_B—X_2—T_{BI}-$ meets test 4 or test 5, precursor in which the T_B and T_{BI} free valences are each saturated with OZ, with Z or with $-Z^I-\underset{|}{N}-Z^{II}$, Z^I and Z^{II} being equal or different and have the Z values as above defined, depending on whether T_B and/or T_{BI} = CO or X, in connection with the values of t, t', tx and txx;
- the C precursor when b0 = 0 is of $-T_c$-Y-H type wherein the T_c free valence is saturated with OZ, Z, or with $-Z^I-\underset{|}{N}-Z^{II}$, Z^I and Z^{II} being as above defined, meets test 5;
- X_{2a} monovalent radical, such that the corresponding precursor of B_1 $-T_{BII}—X_{2a}$ meets test 4 or test 5, precursor wherein the T_{BII} free valence is saturated with OZ or with Z or with $-Z^I-\underset{|}{N}-Z^{II}$, Z^I and Z^{II} being equal or different and having the Z values as above defined, depending on whether T_{BII} = CO or X, in connection with the tI and tII values;

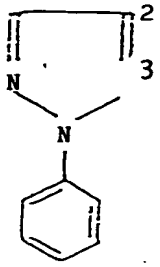
A = R— has the following structure:



wherein in substitution of the hydrogens of the CH groups or of the two hydrogens of the CH_2 groups mentioned in the general formula, the following substituents can be present:

in position 1-2: there may be a double bond;

in position 2-3: there may be the following substituent:



in position 2: there may be Cl, Br;

in position 3: there may be CO, $-O-CH_2-CH_2-Cl$, OH;

in position 3-4: there may be a double bond;

in position 4-5: there may be a double bond;

in position 5-6: there may be a double bond;

in position 5-10: there may be a double bond;

in position 6: there may be Cl, F, CH_3, -CHO;

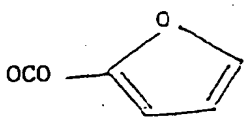
in position 7: there may be Cl, OH;

in position 9: thre may be Cl, F;

in position 11: there may be OH, CO, Cl, CH_3;

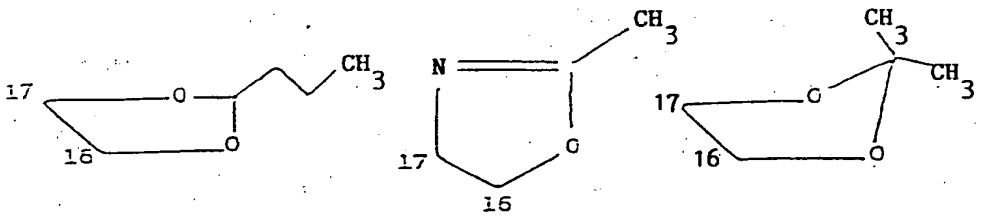
in position 16: there may be CH_3, OH, $=CH_2$:

in position 17: there may be OH, CH_3, $OCO(O)_{ua}(CH_2)_{va}CH_3$, C≡CH or



wherein ua is an integer equal to 0 or 1, va is an integer from 0 to 4;

in position 16-17: there may be the following groups:



R and R', equal to or different from each other, can be hydrogen or linear or branched alkyls from 1 to 4 carbon atoms, preferably R = R' = CH_3;

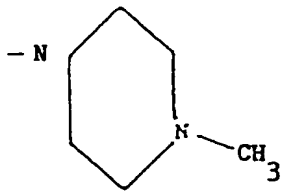
R" is $-(CO-L)_t-(L)_{t2}-(X_O^I)_{t1}-$

wherein t, t1 and t2 are integers equal to or different from each other, equal to 0 or 1, with the proviso that when t = 0 t2 = 1 and when t = 1 t2 = 0, and that t and t1, or t2 and t1, cannot contemporaneously be equal to 0 when A does not contain -OH groups;

the bivalent bridging group L is selected from:

$(CR_4R_5)_{na}(O)_{nb}(CR_4R_5)_{n'a}(CO)_{n'b}(O)_{n''b}(CO)_{n'''b}(CR_4R_5)_{n''a}$

wherein na, n'a, and n''a, equal to or different from each other, are integers from 0 to 6, preferably 1-3; nb, n'b, n''b and n'''b, equal to or different from each other, are integers equal to 0 or 1; R_4, R_5, equal to or different from each other, are selected from H, linear or branched alkyl from 1 to 5 carbon atoms, preferably from 1 to 3; X_0^I is X as above defined, but R_{1c} is a linear or branched alkyl from 1 to 10 carbon atoms, or equal to X_2^I wherein X_2^I is equal to OH, CH_3, Cl, $N(-CH_2-CH_3)_2$, SCH_2F, SH, or



wherein test 4, which must be met by the precursors of B or B_1 with the free valences saturated as above defined, is the following: it is an analytical determination carried out by adding portions of methanol solutions of the precursor of B or B_1 at a 10^{-4} M concentration, to a methanol solution of DPPH (2,2-diphenyl-1-picryl hydrazyl - free radical); after having maintained the solution at room temperature away from light for 30 minutes, it is read the absorbance at the wave length of 517 nm of the test solution and of a solution containing only DPPH in the same amount as in the

test solution; and then the inhibition induced by the precursor towards radical production by DPPH is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the test compound + DPPH and that of the solution containing only DPPH; test 4 is met by B or B_1 precursor compounds if the % inhibition as above defined is higher than or equal to 50%;

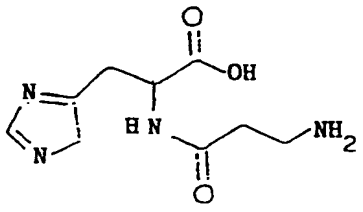
wherein test 5 is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B or B_1 or of C = $-T_C-Y-H$, having the free valence saturated as above indicated, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $Fe^{II}(NH_4)_2(SO_4)_2$; after having thermostatted the solution at 37°C for one hour, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M are added, in the order, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B or B_1 or C = $-T_C-Y-H$ with respect to radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

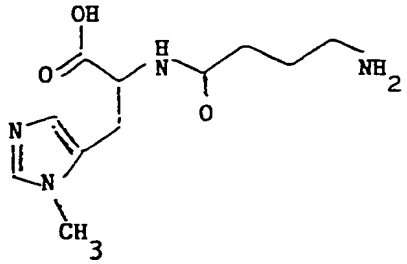
wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B or B_1 or C = $-T_c-Y-H$ is higher than or equal to 50%; provided that in the compounds of formula (I) are excluded the drugs with A = R- when b_0 = 0 and C = $-T_c-Y_0-$ wherein the free valence of Y_0 is saturated as indicated above, s = 1 or 2.

2. Compounds according to claim 1, wherein the precursor compound of B or B_1 which meets test 4, is selected in the following classes:

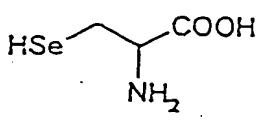
- Aminoacids, selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetyl-penicillamine (CVI), cysteine (CVII), N-acetyl-cysteine (CVIII), glutathione (CIX) or its esters, preferably ethyl or isopropyl ester:



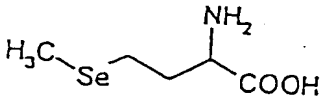
(CI)



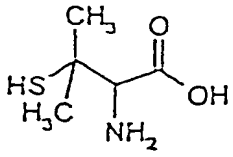
(CII)



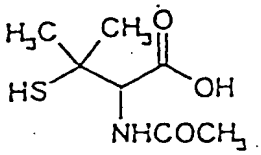
(CIII)



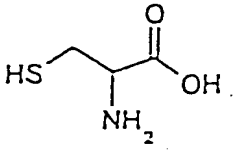
(CIV)



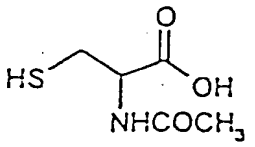
(CV)



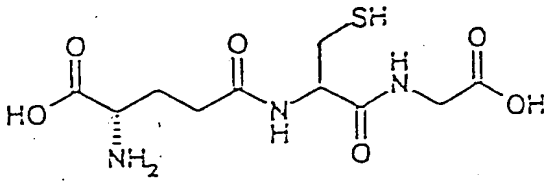
(CVI)



(CVII)

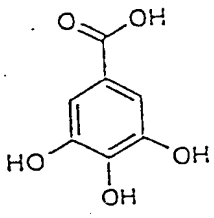


(CVIII)

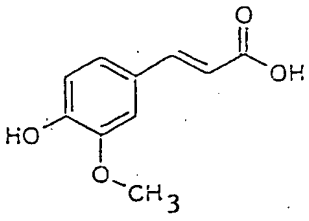


(CIX)

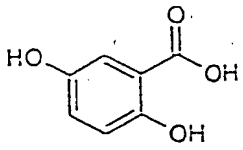
- hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), chlorogenic acid (DIX), kynurenic acid (DX), syringic acid (DXI):



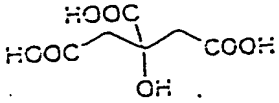
(DI)



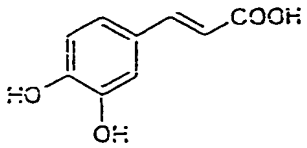
(DII)



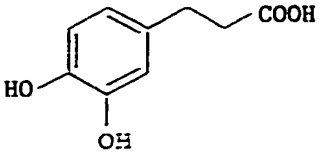
(DIII)



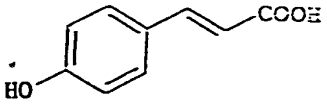
(DIV)



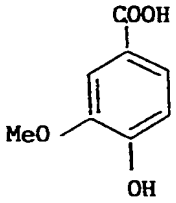
(DV)



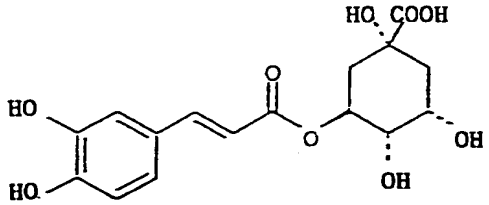
(DVI)



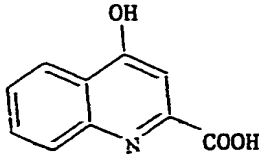
(DVII)



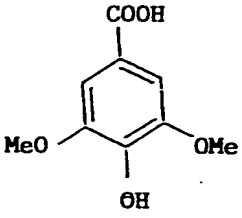
(DVIII)



(DIX)



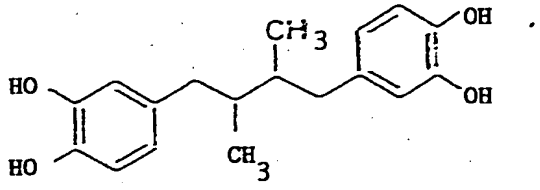
(DX)



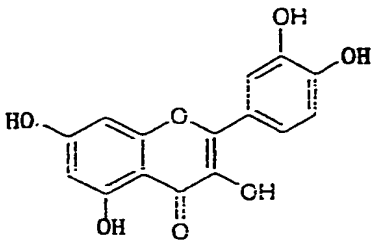
(DXI)

- Aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic

acid (EI), quercetin (EII), catechin (EIII), kaempferol (EIV), sulphurethyne (EV), ascorbic acid (EVI), isoascorbic acid (EVII), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), saccharose (EXIV), vitamin E (EXV), vitamin A (EXVI), 8-quinolol (EXVII), 3-tert-butyl-4-hydroxyanisole (EXVIII), 3-hydroxyflavone (EXIX), 3,5-tert-butyl-p-hydroxytoluene (EXX), p-tert-butyl phenol (EXXI), timolol (EXXII), xibornol (EXXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), 4'-hydroxybutyranilide (EXXV), guaiacol (EXXVI), tocol (EXXVII), isoeugenol (EXXVIII), eugenol (EXXIX), piperonyl alcohol (EXXX), allopurinol (EXXXI), conyferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV), curcumin (EXXXV):



(EI)



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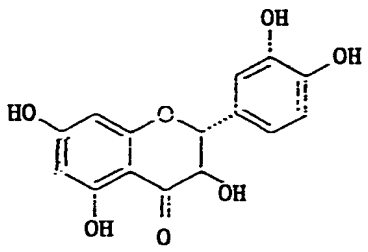
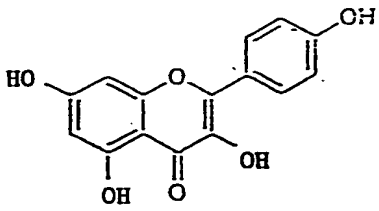
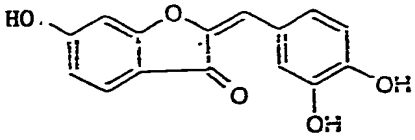


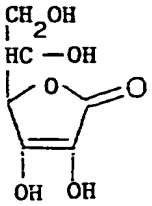
(EIII)



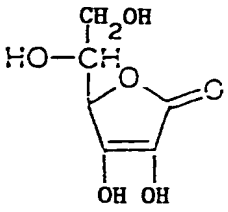
(EIV)



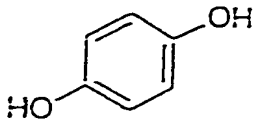
(EV)



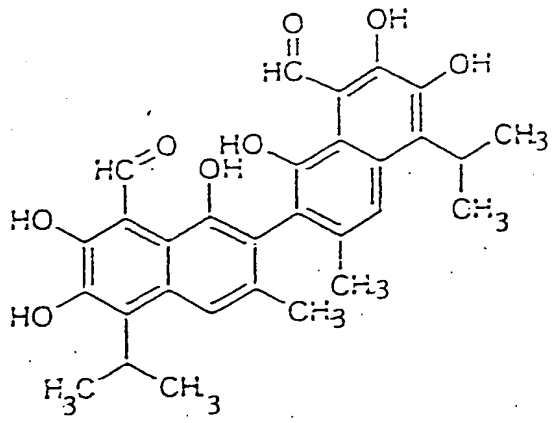
(EVI)



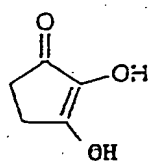
(EVII)



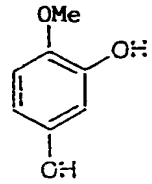
(EVIII)



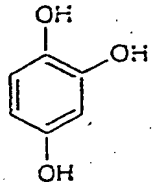
(EIX)



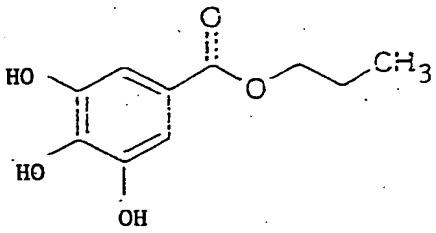
(EX)



(EXI)



(EXII)



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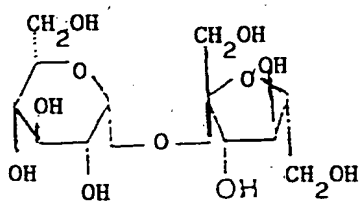

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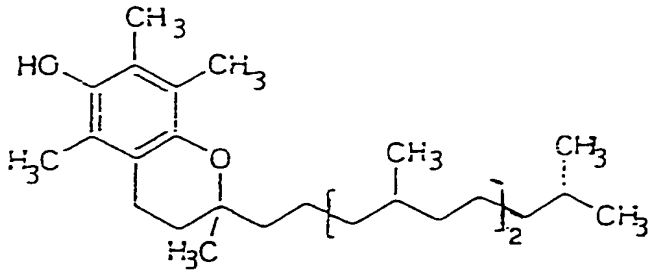

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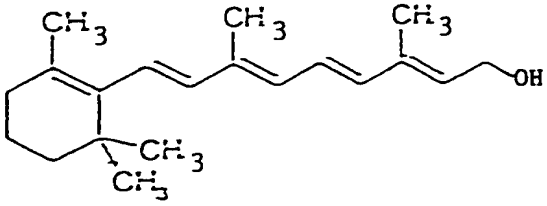
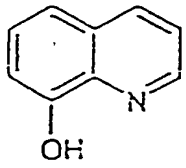
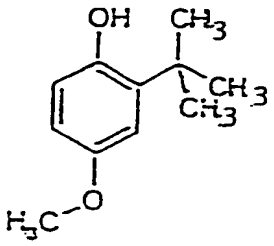


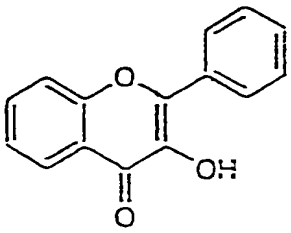
(EXVI)



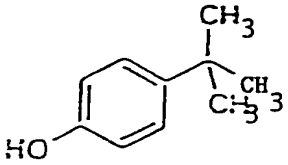
(EXVII)



(EXVIII)



(EXIX)



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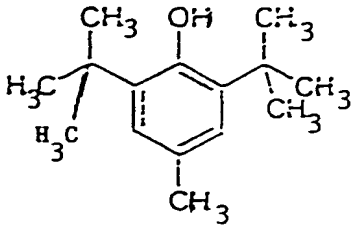
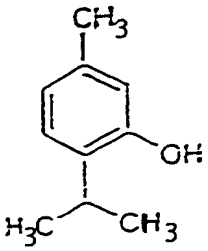
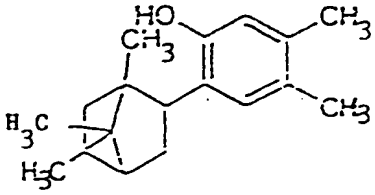


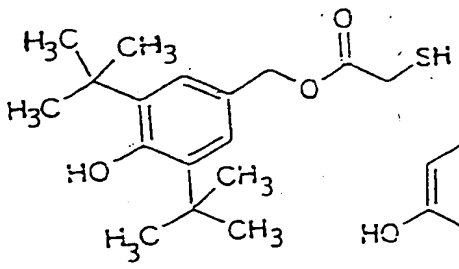
(EXX)



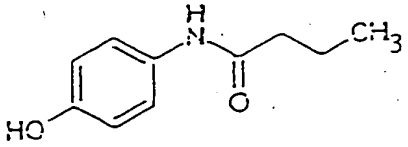
(EXXII)



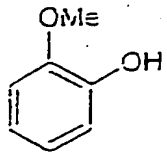
(EXXIII)



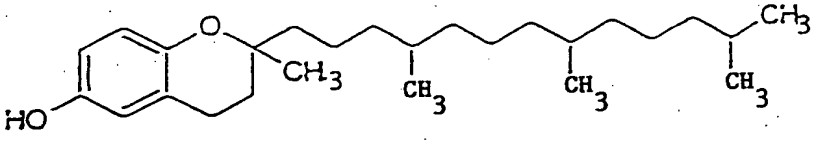
(EXXIV)



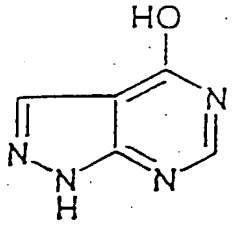
(EXXV)



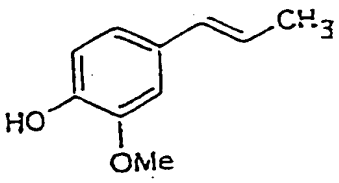
(EXXVI)



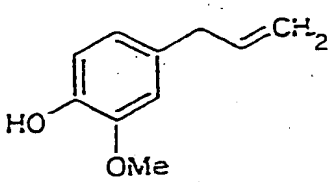
(EXXVII)



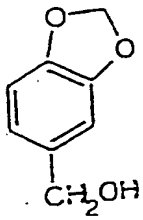
(EXXXI)



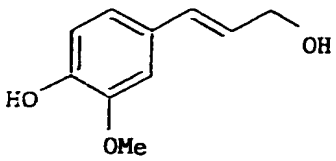
(EXXVIII)



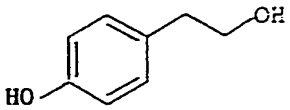
(EXXIX)



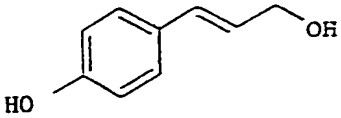
(EXXX)



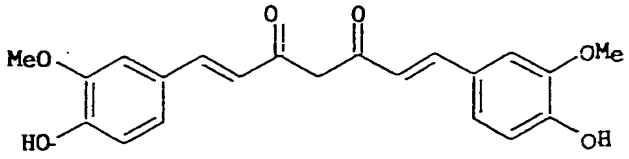
(EXXXII)



(EXXXIII)

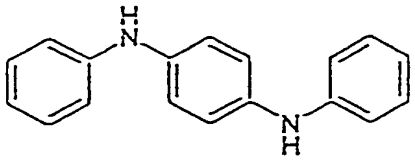


(EXXXIV)

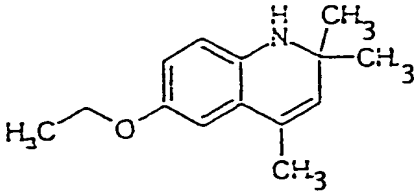


(EXXXV)

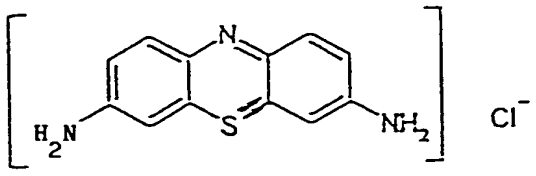
- aromatic and heterocyclic amines, selected from the following: N, N'-diphenyl-p-phenylenediamine (MI), ethoxyquin (MII), thionine (MIII), hydroxyurea (M-IV):



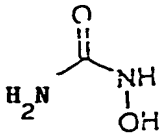
(MI)



(MII)

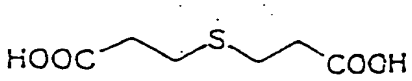


(MIII)

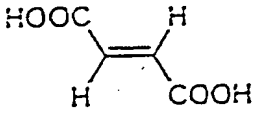


(MIV)

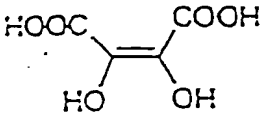
- Compounds containing at least a free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), thioctic acid (NIV), edetic acid (NV), bilirubin (NVI), 3,4-methylendioxycinnamic acid (NVI-I), piperonylic acid (NVIII):



(NI)

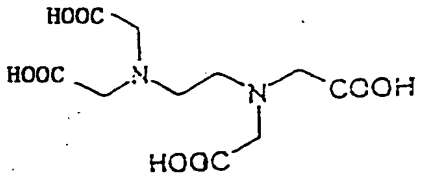


(NII)

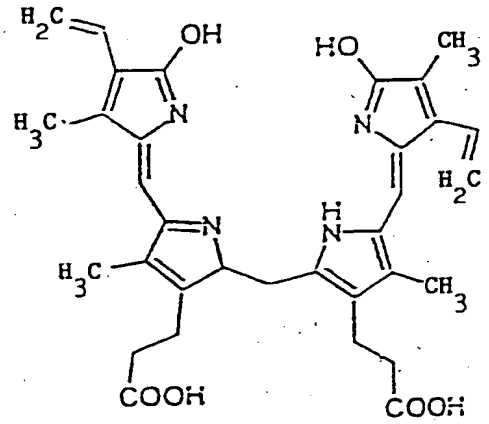


(NIII)

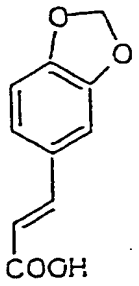
(NIV)



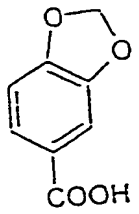
(NV)



(NVI)



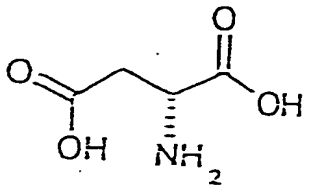
(NVII)



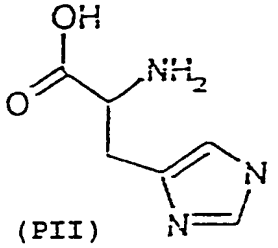
(NVIII)

3. Compounds according to claim 1 wherein the precursor compound of B or B_1 meeting test 5 is selected from the following:

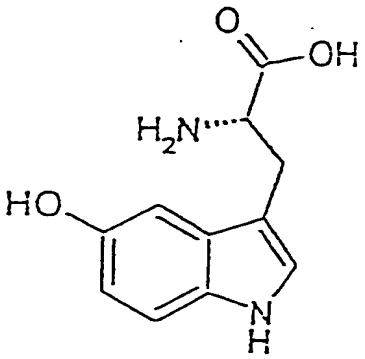
- Aminoacids: aspartic acid (PI), histidine (PII), 5-hydroxytryptophan (PIII), 4-thiazolidincarboxylic acid (PIV), 2-oxo-4-thiazolidincarboxylic acid (PV)



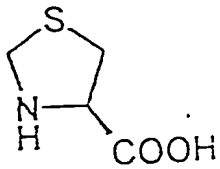
(PI)



(PII)



(PIII)



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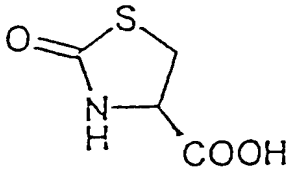
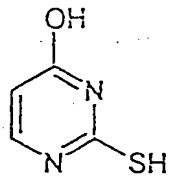
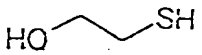


(PV)

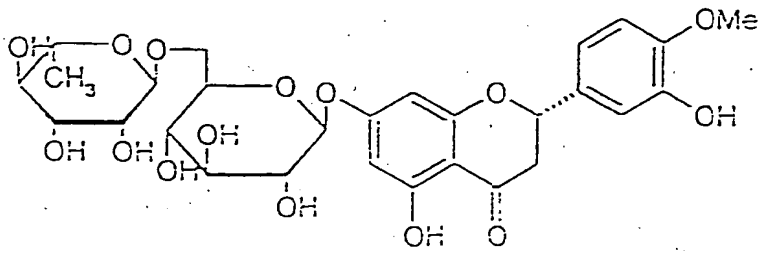
- mono and polyalcohols or thiols: 2-thiouracil (QI), 2-mercaptoethanol (QII), esperidine (QIII), secalciferol (QIV), 1-α-OH vitamin D2 (QV), flocalcitriol (QVI), 22-oxacalcitriol (QVII), the vitamin D3 derivative esterified with the vitamin A radical (QVIII), the formula (QIX) compound, 24,28-methylene-1α-hydroxyvitamin D2 (QX) the compound derived from 1α,25-dehydroxyvitamin D2 (QXI), 2-mercaptoimidazol (QXII)



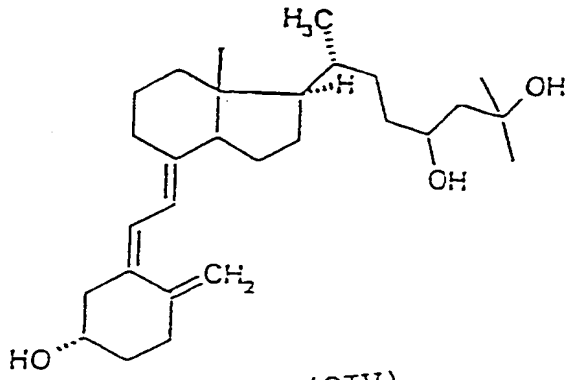
(QI)



(QII)



(QIII)



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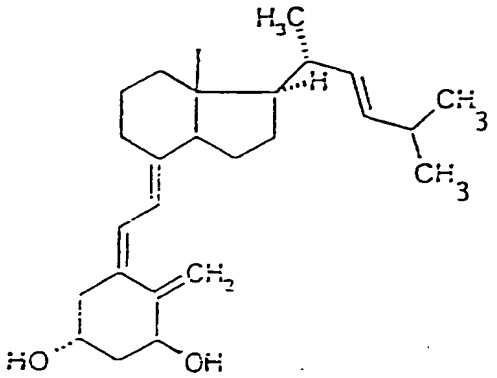
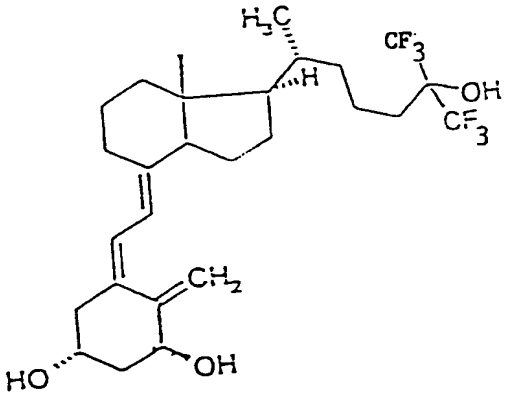
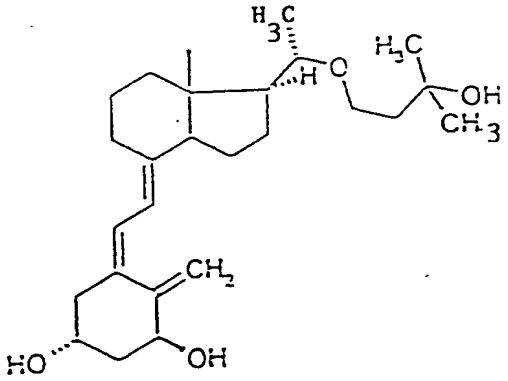


(QV)



(QVI)



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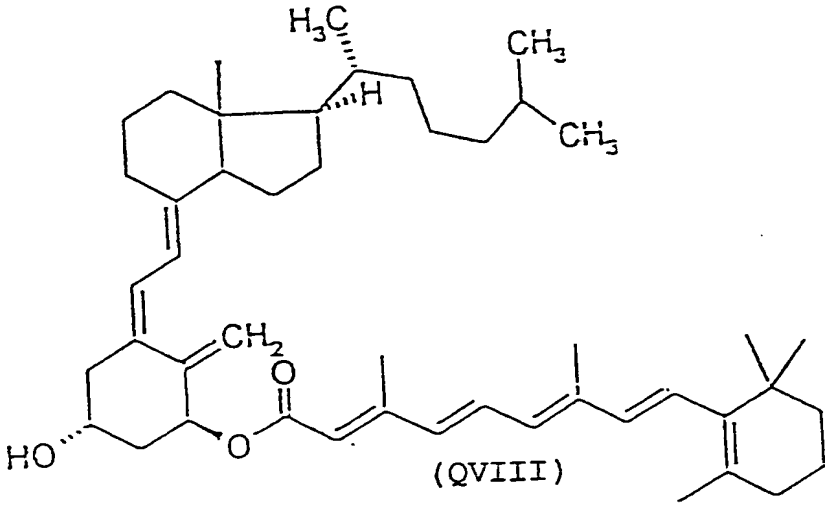
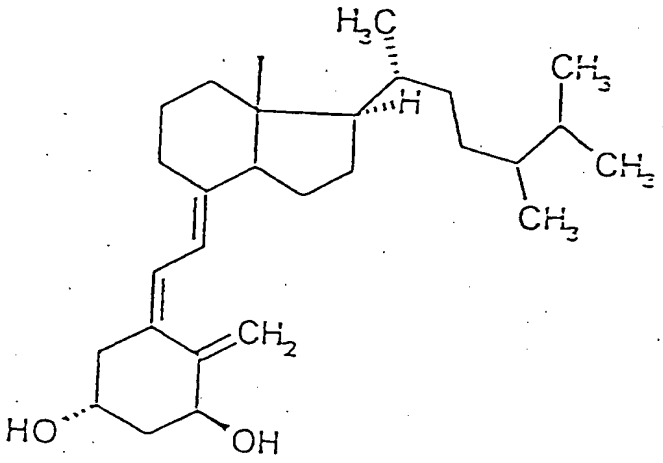


(QVIII)



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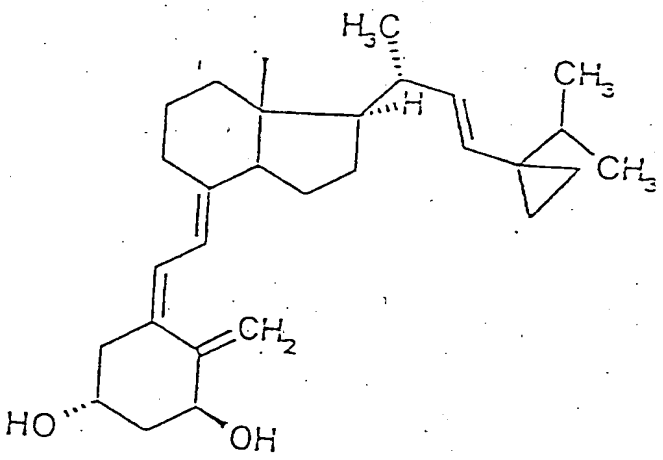
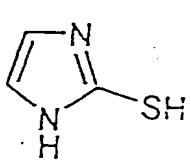
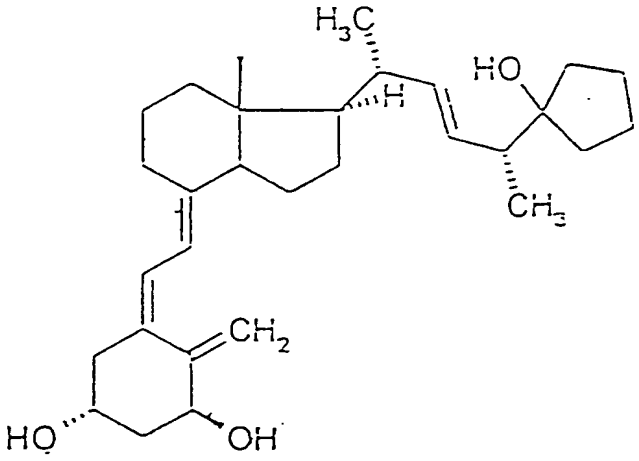


(QX)

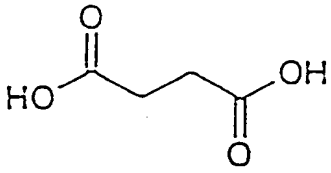


(QXII)



(QXI)

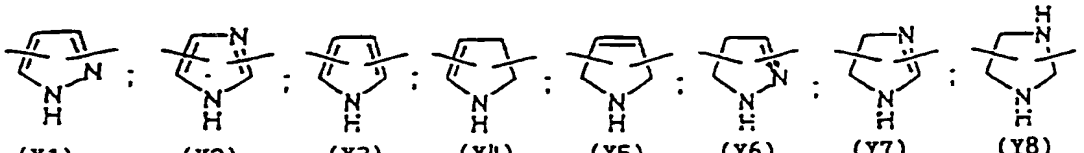
- succinic acid (RI)



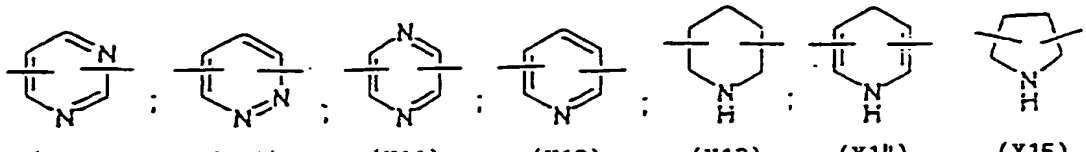
(RI)

4. Compounds according to claims 1-2 wherein the precursors of B and B_1 are those meeting test 4.

5. Compounds according to claims 1-4 wherein Y^3 in formula (III) is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6) (Y7) (Y8)



(Y9) (Y10) (Y11) (Y12) (Y13) (Y14) (Y15)

6. Compounds according to claim 5 wherein Y^3 is Y12 (pyridyl)

substituted in positions 2 and 6.

7. Compounds according to claims 1-6 wherein in the precursor steroids R" = $-CO-CH_2OH$, $-CH(CH_3)-CH_2-CH_2-COOH$.

8. Compounds according to claims 1-7 wherein in the precursor steroids the hydroxyl function is in position 3 and/or in position 11, and/or having in R" an hydroxyl or carboxylic function in terminal position.

9. Compounds according to claims 1-8, wherein the precursor steroids are selected from the following: Budesonide, Hydrocortisone, Alclomethasone, Algestone, Beclomethasone, Betamethasone, Chloroprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone Diflucortolone, Difluprednate, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone Acetonide, Fluocinonide, Fluocortyn Butyl, Fluocortolone, Fluorometholone, Fluperolone Acetate, Fluprednidene Acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol Propionate, Halomethasone, Halopredone Acetate, Hydrocortamate, Loteprednol Etabonate, Medrysone, Meprednisone, Methylprednisolone, Momethasone Furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 25-Diethylaminoacetate, Prednisolone Sodium Phosphate, Prednisone, Prednival, Prednylidene, Rimexolone, Triamcinolone, Triamcinolone

Acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone Propionate, Mazipredone, Tixocortol, Triamcinolone Hexacetonide, Ursodesoxycholic acid, Chenodeoxycholic acid, Mitatrienediol, Moxestrol, Ethynylestradiol, Estradiol, Mestranol.

10. Compounds or salts, or their compositions according to claims 1-9 for use as a medicament; provided that in the compounds of formula (I) are excluded the drugs with A = R- when b_0 = 0 and C = $-T_c-Y_0-$ wherein the free valence of Y_0 is saturated as indicated above, and s = 1 or 2.

11. Use of the compounds or salts, or their compositions according to claims 1-9 for the preparation of drugs for the therapeutic stress oxidative use; in the compounds of formula (I) when b_0 = 0 and C = $-T_c-Y_0$ wherein the free valence of Y_0 is saturated as indicated above, s = 1 or 2, the drug can be A = R-.

12. Pharmaceutical formulations containing as active principle the compounds or their salts of claims 1-9.

D9

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(75) Inventors/Applicants *(for US only)*: **TRESPIDI, Laura** [IT/IT]; Via Lungo Adda, I-26026 Pizzighettone (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

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(54) Title: SOLID DISPERSIONS OF NITRATE ACTIVE PRINCIPLES

(57) Abstract: The invention relates to solid dispersions of nitrate active principles in at least one polymer chosen from the group consisting of polyvinyl pyrrolidone, cellulose derivatives or polyethylene glycol, their production processes and pharmaceutical formulations including said dispersions.

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(54) Title: SOLID DISPERSIONS OF NITRATE ACTIVE PRINCIPLES

(57) Abstract: The invention relates to solid dispersions of nitrate active principles in at least one polymer chosen from the group consisting of polyvinyl pyrrolidone, cellulose derivatives or polyethylene glycol, their production processes and pharmaceutical formulations including said dispersions.

Solid dispersions of nitrate active principles

FIELD OF THE INVENTION

The present invention relates to solid dispersions of nitrate active principles characterized by an increased dissolution rate and/or apparent solubility of said active principles and to a method for their production.

STATE OF THE ART

The applicant has developed a number of active principles, characterized by the presence in their structure of a nitro group, having remarkably advantageous pharmacological properties. These active principles are described in the patents: EP670825, EP722434, EP759899, EP609415, US5703073, and in the patent applications WO98/15568, WO98/21193, WO00/51988, WO00/61537, WO00/61541, WO00/61604, WO00/25776, MI99A001817.

Unfortunately, the utility of many of the above mentioned active ingredients is limited by their scarce solubility in water, which results in an insufficient and irregular absorption and a slow onset of the pharmacological action. This last aspect is particularly problematic in case of active ingredients such as, for instance, antinflammatory active ingredients and/or analgesics for which a rapid onset of the therapeutic action is of fundamental importance.

Thus, there is as need to develop new pharmaceutical formulations for the administration of nitrate active principles which, compared with traditional formulations, are characterized by an improved bioavailability and a faster onset of action.

It is known that the dissolution rate of poor water-soluble drugs can be increased by their conversion to the corresponding amorphous forms. A technique which can be used to this purpose is the formation of a solid dispersion of the active agent in an inert matrix, usually of polymeric nature. Nevertheless, this technique does not always allow to obtain the amorphous form and consequently the increase in dissolution rate of the active agent. Several parameters such as, for instance the interactions between the polymer and the active ingredient, the ratio between then and the production technique adopted influence the chemical-physical features of the solid dispersion obtained. Thus, for each particular active ingredient it is necessary to select both the polymer and the operative conditions for the preparation of the dispersion that lead to the conversion to the amorphous form.

SUMMARY OF THE INVENTION

The inventors have now found that it is possible to obtain an increase in the dissolution rate and/or the apparent solubility and consequently in the bioavailability of nitrate active principles by forming solid dispersions of said active principles characterized in that the inert matrix includes at least one polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

Therefore, the present invention refers to solid dispersions comprising at least one nitrate active principle and a hydrophilic polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

DESCRIPTION OF THE FIGURES

Figures 1, 2 and 3 show the thermograms of the crystalline form and of the amorphous solid dispersion according to the present invention of the following derivatives:

4- acetylaminophenyl ester of 4 nitroxybutanoic acid (NCX701)

2- (acetyloxy-benzoic-acid-3-nitroxymethyl) phenyl ester (NCX 4016)

(hydroxycortisone 21-[(4'nitroxymethyl)benzoate] (NCX 1022)

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to solid dispersions comprising at least one nitrate active ingredient and a hydrophilic polymer chosen among polyvinyl pyrrolidone, preferably having a molecular weight comprised between that of the polyvinyl pyrrolidone K17 and that of polyvinilpyrrolidone K30, cellulose ethers and polyethylene glycol, preferably having a molecular weight higher than that of PEG 1000, and more preferably PEG with a molecular weight higher than that of PEG 1500 and lower than that of PEG 6000. Among the cellulose ethers particularly preferred is the hydroxypropylmethylcellulose, preferably having a viscosity at 20°C, in a 2% aqueous solution, lower than 50 cPs, and preferably hydroxypropylmethylcellulose with viscosity comprised between 5 and 50 cPs.

By "nitrate active principles" it is meant compounds having formula (I).

$$A\text{-}X_1\text{-}L\text{-}(W)_p\text{-}NO_q \qquad (I)$$

wherein:

p is an integer equal to 1 or 0;

q is an integer equal to 1 or 2;

A=R-T_1-, wherein **R** is the radical of a pro-drug having formula **R-T_1-Z**, chosen among the therapeutic classes of drugs reported here after, wherein

Z is **H, OH, NH_2, NHR_3, $N(R_3)_2$,** wherein R_3 is a linear or branched C_1-C_5 alkyl radical

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein X = an oxygen atom, a sulphur atom or NR_2 wherein R_2 is hydrogen or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integer and equal to zero or 1, provided that t = 1 when t' = 0; t = 0 when t' = 1;

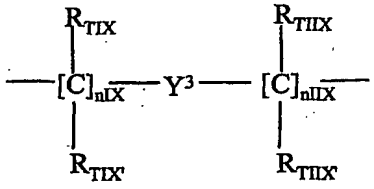
$X_1 = -T_B-Y-T_{BI}$ wherein T_B and T_{BI} are the same or different

$T_B = (CO)$ when t = 0, $T_B = X$ when t' = 0, being X as above defined;

$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx are 0 or 1; with the proviso that tx = 1 when txx = 0; tx = 0 when txx = 1; X is as above defined;

Y is a bivalent bridging group chosen among the following:

1)



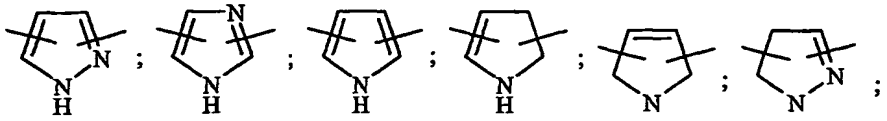
wherein:

nIX is an integer comprised between 0 and 3, preferably 1;

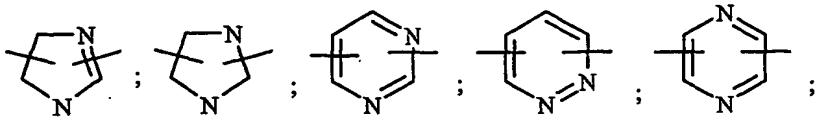
nIIX is an integer comprised between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal or different from one another, are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

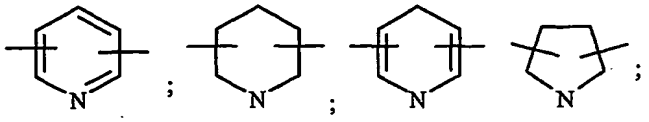
Y^3 is a saturated , unsaturated or aromatic heterocyclic ring having 5 or 6 atoms and containing one or two nitrogen atoms, Y^3 is preferably chosen among the following bivalent radical:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



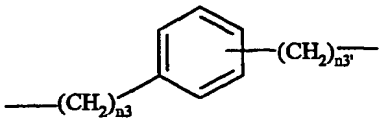
(Y12) (Y13) (Y14) (Y15)

wherein (Y12) is preferred ;

2) an alkylene group R' wherein R' is C_1-C_{20} linear or branched when possible, having preferably 2 to 6 carbon atoms, optionally substituted with at least one of the following groups: $-NH_2$, -OH or $-NHCOR_3$, wherein R_3 is a linear or branched C_{1-5} alkyl;

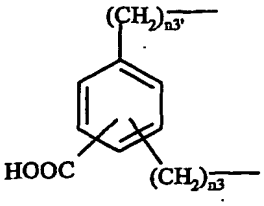
3) a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chains R', wherein R' is as defined above, and at least one carbon atom of the cycloalkylenic ring can be optionally substituted with etheroatoms.

4)



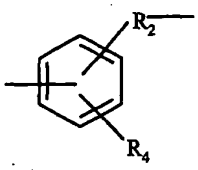
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

5)



wherein n3 and n3' have the above indicated meaning,

6)

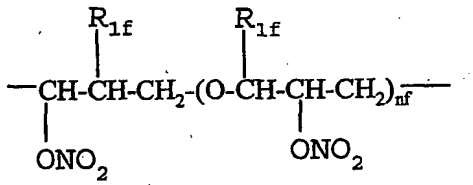


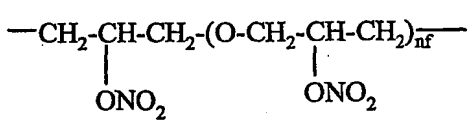
wherein

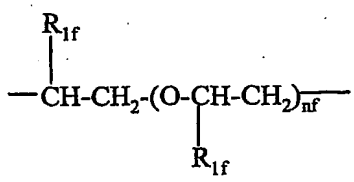
R_4 is hydroxy, hydrogen, alkoxy R_5O- wherein R_5 is a linear, branched or cyclic $C_{1\text{-}10}$ alkyl group, preferably R_5 is a methyl group;

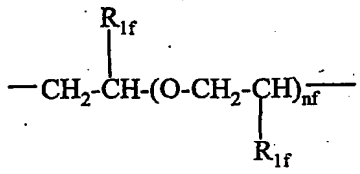
R_2 is a linear or branched C_2-C_{10} alkenyl group, including at least one double bond, preferably R_2 is the ethenylene group (-CH=CH-);

7)









wherein R_{1f} = H, CH_3 and nf is an integer from 0 to 6; preferably from1 to 4;

8) or Y is the bivalent radical whose precursor Z-T_B-Y-T_{BI}-Z, wherein Z is as defined above and it is chosen among the following compounds:

aspartic acid, histidine, 5-hydroxytryptophan, 2-thiouracil, 2-mercaptoethanol, hesperidine, secalcipherol, 1-α-OH-Vitamin D2, flocalcitriol, 22-oxacalcitriol, 24,28-

methylen-1α-hydroxyvitamin D2, succinic acid, L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione, gallic acid, ferulic acid, gentisic acid, citric acid, caffeic acid, hydrocaffeic acid, p-coumaric acid, vanillic acid, chlorogenic acid, kynureic acid, siringic acid, nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfuretin, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydrohydroxyquinone, propyl gallate, saccharose, 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate, allopurinol, conyferyl alcohol, 4-hydroxyphenethyl alcohol, p-coumaric alcohol, curcumin, N,N'-diphenyl-p-phenylenediamine, thionine, hydroxyurea, 3,3'-thiodipronic acid, fumaric acid, dihydroxymaleic acid, N-methylendiethanolamine, thiodiethylenglycol, 1,4-dioxane-2,6-dimethane, tetrahydropyran-2,6-di-methanol, 4H-pyran-2,6-di-methanol, cyclohexene-1,5-dimethanol, 1,4-dithian-2,6-dimethanol, thiophene-2,5-di-methanol, oxazole-2,5-di-methanol.

L= covalent bond, or **L = X**, **X** being as defined above, **L = (CO)**

W = Y_T-X- wherein Y_T has the same meanings of **Y**, but is different from **Y**,

R-T_1-Z is chosen among the following drugs:

- Non steroidal anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, alclofenac, alminoprofen, amfenac, ampiroxicam, balsalazide, bendazac, bermoprofen, α-bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac, CS-670, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, mechlofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxifenbutazone, parsalmide, pemedolac, perisoxal, phenyl acetylsalicilate, pirazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamido-O-acetic acid, saliciylsulforic acid, salsalate, sulindac, suprofen, suxibuzone, tenidap, tenoxicam, thiaprofenic acid, thiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepi-

rac, tomoxiprol,

Analgesics: paracetamol, acetaminosalol, aminochlorthenoxazin, acetylsalicilic acid, 2-amino-4-picoline, acetylsalicylsalicilyc acid, anileridine, benoxaprofen, benzylmorphine, 5-bromosaliciylic acid acetate, bucetin, buprenorfine, butorfanol, capsaicin, cincofenol, ciramadol, clometacine, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimefeptanol, dipyrocetyl, eptazocine, etoxazen, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodon, hydromorone, hydroxypetidine, ibufenac, p-lactophenetide, levorfanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorfanol, normorphine, oxycodone, oxymorphon, pentazocine, fenazocine, fenocoll, fenoperidine, fenilbutazone, phenylsalicylate, phenilramidol, salicin, salicylamide, tiorphan, tramadol, diacereine, actarit;

- Steroids: chenodeoxycholic acid, ursodeoxycholic acid, alclomethasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chlorprednisone, clobetasol, clobethasone, clocortolone, cloprednol, corticosteron, cortisone, cortivazol, deflazacort, desonide, desoximethasone, dexamethasone, diflorasone, diflucortolone, difluprednate, estradiol, ethynilestradiol, fluazacort, flucloronide, flucortyn butyl, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortolone, fluoromethólone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halomethasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, mestranol, metilprednisolone, mitatrienediol, mometasone furoate, moxestrol, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisone, prednival, prednylidene, rimexolone, 21-acetoxy-pregnenolone, triamcinolone hexacetonide, triamcinolone acetonide, triamcinolone, tixocortol;
- Bronchodilatory drugs: acephilline, albuterol, bambuterol, bamiphylline, bevonium methyl sulfate, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxetedrine, diphylline, ephedrine, epinephrine, eprozinol, etaphedrine, ethylnorepinephrine, etophylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetarine, isoprotenerol, mabuterol, metaprotenerol, oxitropium bro-

mide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-theobromoacetic acid, thiotropium bromide, tretoquinolol, tulobuterol, oxybutinyn, zaprinast.

- Expectorants and mucolitic agents: ambroxol, bromexine, domiodol, erdosteine, guaiacol, guaifenesine, glycerol iodurate, letosteine, mesna, sobrerol, stepronin, terpin, thiopronin;
- Anti-asthmatic, antiallergic and antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, hystamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, bromexine, formoterol;
- ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naftopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;
- β-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronetalol, propranolol, sotalolol, sulfinalolol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;
- Drugs for vascular disorders: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betaistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, heparine, dalteparin, dipiradamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, lamifiban, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, prenilamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinophedrine, tinzaparin, triflusal, xanthinol niacinate, fenilpropanolamine, midodrine;
- Antidiabetics: acarbose, carbutamide, glibomuride glybuthiazol, miglitol, repaglinide, troglitazone, 1-buthyl-3-methanyl-urea, tolrestat, nicotinamide;
- Antitumoral drugs: ancitabine, anthramicine, azacitidine, azaserine, 6-azauridi-

ne, bicalutamide, carubicine, carzinophilin, chlorambucil, chlorozotocin, citarabine, daunorubicine, defosfamide, demecolcine, denopterine, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicine, droloxifene, edatrexate, eflornithine, enocitabine, epirubicine, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracyl, gemcitabine, hexestrol, idarubicine, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, micophenolic acid, ninopterine, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamicine, podofillic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, tiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicine;

- Antiulcer drugs: ε-acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazol, ornoprostil, pantoprazol, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;
- Antihyperlipidemic drugs: atorvastatine, cilastatine, dermostatine, fluvastatine, lovastatine, mevastatine, nistatine, pentostatine, pepstatine, privastatine sodium salt, simvastatine;
- Antibacterial drugs: amdinocillin, amoxicillin, ampicillin, apalcillin, apicyclin, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazoline, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, cefoxanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracicline, cinoxacine, clavulanic acid, clofoctol, clometocilline, cloxacilline, cyclacilline, cycloserine, demeclocicline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, me-

clocycline, meropenem, metampicillin, metacicline, meticillin sodium salt, mezlocillin, minocicline, moxalactam, mupirocin, myxin, negamycine, novobiocin, oxacillin, pamipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, pheneticillin potassium salt, pipaciclyne, piperacillin, pirlimycin, porfiromycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidine, argininsa, arbekacin, apramycin, amikacin, azithromycin, bacampicillin, cefcapene pivoxil, cefpodoxime proxetil dapsone, deoxydihydrostreptomycin dibekacin, etambutol, flumequine, guamecycline, nifurpirinol, nifurprazine, nitroxoline, glyconiazide, isoniazide, opiniazide, mupirocin, negamycin, netilmicyn, pipacycline, fortimycins, gentamycin, ibostamycin, lincomycin, micronomycin, midecamycin, miokamycin, oleandomycin, paromomycin, rosaramycin, sisomycin, streptomycin, tobramycin, trospectomycin, claritromycin, diritromycin, enviomycin, erithromycin, josamycin, midecamycin, miocamycin, rifabutine, rifamide, rifamycin, rifaxymine, rokitamycin, spiramycin, troleandromycin, viomycin, virginiamycin; p-aminosalicylic acid, benzilpenicillinic acid, acetil sulfametossipirazine, acediasulfone, 4-sulfanylamidosalicylic acid, 4,4'-sulfinyldianiline, 4'-(methylsulfamoyl)sulfanylanilide, 2-p-sulfanilylanilinoethanol, N-sulfanilyl-3,4-xylamide, p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, salazosulfadimidine, salinazid, succisulfone, sulfabenzamide, sulfacetamide, sulfachlorpiridazine, sulfachrysoidine, sulfacitine, sulfadiazine, sulfadicramide, sulfadimetoxine, sulfadoxine, sulfaetidol, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfametazine, sulfametizol, sulfamethomidine, sulfametoxazol, sulfametoxypiridazine, sulfamethyltiazol, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanylamide, sulfanylilurea, sulfaperine, sulfafenazol, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfatiazol, sulfathiourea, sulfisomidine, sulfisoxazol, sultamicillin, tiazosulfone, mafenide, clofazimine, carbomycin, clomocycline, meclocycline, metampicillin, meticillin, metronidazole, mezlocillin, moxalactam, oxytetracycline, piromidic acid, pivampicillin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, grepafloxacin, lomefloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, rifanpin, rufloxacin, ta-

lampicillin, trovafloxacin, tosufloxacin, sparfloxacin;

- Antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxine, ribavirine, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;
- Inhibitors of bone reabsorption: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;
- Drugs for dementia: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

When the compounds include at least one asymmetric carbon atom, the products can be used in racemic mixture or in form of single enantiomer.

The active principle in the solid dispersions of the invention is in amorphous form. By "amorphous form" of a compound it is meant a solid form of that compound that when subjected to DSC analysis does not show the melting endothermic peak.

When the active principle is in the solid dispersions of the present invention it is characterized by a higher dissolution rate and therefore a higher bioavailability than in the non dispersed form. As it will be shown in detail in the following examples, a particularly high increase in the dissolution rate occurs when the hydrophilic polymer used in the dispersion is polyvinylpyrrolidone. Thus, the use of the polyvinylpyrrolidone as the hydrophilic polymer is particularly preferred when a very fast release of the active agent is desired.

Preferably the solid dispersions of the present invention comprise one or more nitrate active principles in amounts comprised between 5% and 60% w/w and preferably between 15% and 40% w/w and the hydrophilic polymer in amount ranging from 50% to 90%, preferably between 70% and 85% w/w.

Optionally, the solid dispersions of the present invention comprise also pharmaceutically acceptable excipients such as, for instance, wetting and solubilising agents in amount preferably ranging from 2% to 20%. Preferably the solubilising agents are surfactants, and among them most preferred are polysorbates, esters and ethers of polyethylen glycols, polihydroxylated castor oil and sodium laurylsul-

phate. The solid dispersion of the invention can be produced by using processes known in the art such as, for instance, the methods based on co-precipitation, the methods based on melting, which consist in melting together the active agent and the carrier and then cooling the melted mass, among them it is mentioned in particular "snap-cooling" where the cooling of the melted mass is carried out on stainless steel plates, "injection molding" where the molten mass is injected into a mould, hot melt extrusion where the active principles and the carrier mixture while flowing through the extruder is contemporaneously melted, homogenized and then extruded in the form of pellets, granules and other intermediates to be used for the production of tablets (the advantage of this technique is that the mixture is subjected to high temperatures just for one minute and it is therefore suitable for active agents sensible to high temperatures), "spray congealing", where cooling of the melted mass is carried out by freezing, and the methods based on solvent evaporation, consisting in dissolving the active agent and the carrier in the same solvent, or in forming an emulsion of the active agent and of the carrier in the solvent. Among these methods a technique allowing to easily and quickly obtain solid dispersions is "spray drying". An especially preferred process for the production of the solid dispersions of the invention is a spray-drying process comprising the following steps:

a) dissolving the active principle in a solution or suspension of the hydrophilic polymer;

b) spraying the mixture obtained in step (a) through the standard nozzle of a sprayer at a flow rate ranging from 5 to 60 ml/min and at a temperature of the inlet air comprised between 50°C and 130°C.

The solution or suspension of step a) can be realized in solvents such as, for instance, water, ethanol, isopropyl alcohol, methylen chloride, butanol, cyclohexane, hexane, acetone or mixture thereof. The choice of the solvent depends on the characteristics of solubility of the active agent which has to be dissolved.

The concentration of polyvinyl pyrrolidone, hydroxypropylmethylcellulose or polyethylene glycol in said solution or suspension is comprised between 1% and 10% w/v and preferably between 2.5% and 7.5% w/v.

The active principle ingredient is added to said solution or suspension in such an

amount to obtain a concentration comprised between 0.1% and 10% w/v and preferably between 0.5% and 7.5% w/v.

Optionally, at least one of the above mentioned pharmaceutically acceptable excipients can be added to the solution or suspension in such an amount as to obtain a concentration of said excipients comprised between 0.01% and 10% w/v and preferably between 0.05% and 5% w/v.

The spraying carried out in step b) is preferably carried out at a flow rate comprised between 5 and 60 ml/min and at an inlet air temperature comprised between 50°C and 130°C.

The solid dispersions of the present invention can be administrated as such, in form of powder, or used, for instance, for the production of granulates, tablets, capsules, suspensions, solutions, suppositories and aerosols.

Therefore, a further object of the present invention are pharmaceutical formulations for oral, parenteral, rectal, (trans)dermic or (trans)mucosal administration of the nitrate active principles comprising the solid dispersions of the invention.

If compared to conventional formulations, the formulations of the invention allow to improve the bioavailability and the onset of action of the nitrate active principles.

The invention will be now explained in detail by the following examples to be considered as a not limiting explanations of the invention.

EXAMPLE 1

Preparation of solid dispersions of the 4- acetylaminophenyl ester of the 4-nitroxybutanoic acid (NCX701).

A solution in methylene chloride/ethanol (90/10 v/v) including 0.8823% w/v of 4-acetylaminophenyl ester of the 4-nitroxybutanoic acid and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. This has then been sprayed through the standard nozzle (inner diameter 1 mm) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) at a flow rate of 20 ml/min while keeping an inlet hot air temperature of 60°C.

The obtained product has then been analysed by scanning calorimetry using a DSC T.A.2910 of T.A. INSTRUMENTS, with a heating interval and scanning rate of 10°C/min. under constant nitrogen flow. The obtained thermogram, reported in Figure 1, shows that the analysed product is amorphous. In fact no thermic event

is detected in the considered temperature interval and in particular in correspondance with the melting temperature of the 4-acetylaminophenyl ester of the 4 nitroxybutanoic acid, at 78°C.

EXAMPLE 2

Evaluation of the dissolution rate of 4-acetylaminophenyl ester of 4 nitroxybutanoic acid in solid dispersion

The dissolution rate of the active principle of the solid dispersion produced in Example 1 has been evaluated, in comparison with the dissolution rate of the pure active principle in micronized form with the paddle method, described in F.U.X., using the following conditions:

dissolution means: distilled water

temperature: 37°C±0.5

stirring rate: 100 r.p.m.

The quantity of active ingredient released has been evaluated by UV spectrophotometry at a wavelength of 240 nm. The following table shows the average of the results obtained from three determinations, expressed as percentage of active principle dissolved at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion
5	17.8	100
10	38.8	100
15	52.1	100
20	60.7	100
25	67.5	100
30	72.4	100
35	76.4	100
40	79.7	100
45	82.6	100
50	85.2	100
55	87.3	100
60	94.9	100

As it can be observed from the table, while the active principle as such is characterized by a slow dissolution in water, when this is in the form of a solid dispersion in polyvinyl pyrrolidone its dissolution is immediate, occurring in less than five minutes.

EXAMPLE 3

Preparation of solid dispersions of 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid (NCX4016)

Two solutions in methylene chloride/ethanol (90/10 v/v) having the following compositions have been prepared:

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of polyvinyl pyrrolidone K25;

2.1 % w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/p of polyvinyl pyrrolidone K25;

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of hydroxypropylmethylcellulose.

The solutions have then been sprayed as described in Example 1. The product obtained has been analysed by scanning calorimetry using a device described in the preceding example. The thermogram obtained, reported in Figure 2, shows that the analysed product is amorphous. In fact no thermic event is detected in the considered temperature interval and in particular in correspondance with the melting temperature of the 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid, at 63.52°C.

EXAMPLE 4

Determination of the dissolution rate of NCX4016 in solid dispersion

The dissolution rate of the solid dispersion produced in the example 3 has been compared with the dissolution rate of the pure NCX4016 in micronised form using the paddle method described in F.U.X., according to the following operating conditions T = 37°C±0.5°C, stirring rate:150 rpm, dissolution means: 1% sodium lauryl sulphate solution, dissolution volume: 900 ml.

The quantity of NCX4016 released has been spectrophotometrically evaluated in continuous at a wavelength 232 nm. The following table shows the average of the results obtained from 3 determinations, expressed as percentage of active principle dissolved at different time intervals.

TIME (minutes)	NCX4016 micronized	NCX4016 Solid dispersion 1	NCX4016 Solid dispersion 2	NCX4016 Solid dispersion 3
5	17.9	98.2	98.1	27.3
10	39.2	99.9	99.2	65.7
15	53.5	100	100	81.1
20	60.7	100	100	90.2
25	71.4	100	100	92.4
30	77	100	100	94.1
35	80.9	100	100	94.7
40	84.4	100	100	94.9
45	87	100	100	95.4
50	88.9	100	100	95.4
55	90.6	100	100	95.4
60	91.4	100	100	95.4

Also in this case, as it can be observed from the table, the dissolution rate of the active principle in all the three solid dispersions is higher than that of the active principle in pure form. Moreover, when the active principle is dispersed in polyvinyl pyrrolidone, the increase in the dissolution rate is remarkably high and an almost immediate release is observed.

EXAMPLE 5

Evaluation of the dissolution rate of 3-(nitroxymethyl)phenyl ester of the 2-acetoxybenzoic acid (NCX4016) in solid dispersion under condition of supersaturation

Three samples of microspheres have been exactly weighed so as to have a con-

tent of nitroaspirine of 30 mg. This quantity corresponds to about 4 times the solubility in water of the active principle.

The dissolution rate of the active principle from the above mentioned 3 solid dispersions has been compared with the dissolution rate of the pure active principle in micronized form, with the paddle method, described in F.U.X. using the following conditions:

dissolution means: distilled water

temperature: 37°c±0.5

stirring rate: 100 r.p.m.

volume = 900 ml

The quantity of NCX 4016 released has been evaluated spectrophotometrically in continuous at a wavelength 232 nm.

The samples have been taken by means of a peristaltic pump at 5 minutes intervals and for the total time of one hour.

The following table shows the average of the results obtained from three determinations, expressed as percentage of dissolved active principle at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion 2
5	n.r.[a]	55.1
10	n.r.[a]	54.3
15	n.r.[a]	51.8
20	n.r.[a]	48.7
25	n.r.	46.9
30	Nr.[a]	44.7
35	n.r.[a]	42.8
40	n.r.[a]	40.8
45	n.r.[a]	38.6
50	n.r.[a]	37.3
55	n.r.[a]	35.7
60	n.r.[a]	34.3

a: spectrophotometrically not detectable

The quantity of active agent NCX4016 dissolved after 5 minutes is about twice the solubility of the active ingredient in the dissolution means.

EXAMPLE 6

Preparation of solid dispersions of HCT 1026 (2-fluoro-α-methyl[1.1'biphenyl]4-acetic acid-4nitrooxy butyl ester

Two solutions in methylene chloride/ethanol (90/10 v/v) with the following compositions have been prepared:

HCT 1026 0.44% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

HCT 1026 0.88% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

The solutions have then been sprayed under the same conditions used in Example 1.

EXAMPLE 7

Evaluation of the dissolution rate of the HTC1026 in solid dispersion

The dissolution rate of the HCT 1026 from the solid dispersion 1 has been evaluated, in comparison with the dissolution rate of the pure active ingredient, with the paddle method described in F.U.X. In detail, 50 mg of the solid dispersion 1 and 7.5 mg of pure active ingredient are placed in a thermostatic container at 37°C±0.5°C in 900 ml of distilled water including 1% w/v of SDS and kept under stirring at 150 rpm. The quantity of HCT 1026 passed into the solution is continuously spectrophotometrically determined in continuous at a wavelength of 245 nm.

In the following table the average of the results obtained from three determinations is reported, expressed as percentage of active principle dissolved at different time intervals:

TIME (minutes)	Pure HCT 1026	Solid dispersion 1
5	5.84	81.04
10	16.74	84.74
15	23.6	85.2
20	29.84	86.13
25	32.78	85.67
30	37.92	85.85
35	42.57	86.31
40	47.46	86.68
45	54.94	86.78
50	58.98	86.78
55	58.98	87.42
60	64.72	87.79

The results obtained show also in this case that when the active agent is in solid dispersion in polyvinyl pyrrolidone its dissolution speed is much higher than the one of the active agent in non dispersed form, and the release of more than 80% of the active principle is observed in less than 5 minutes.

EXAMPLE 8

Preparation of solid dispersions of NCX 1022 (hydroxycortisone 21-[(4'-nitroxymethyl)benzoate]

A solution of methylene chloride/ethanol (90/10 v/v) including 0.44% w/v of NCX 1022 and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. It has then been sprayed through the standard nozzle (1 mm inner diameter) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow rate of 20 ml/min keeping a temperature of the inlet hot air of 60°C.

The product obtained has then been analyzed through scanning calorimetry by using the device described in the preceding examples. The thermogram obtained, reported in Figure 3, shows that the analysed product is amorphous and degrades at a temperature lower than 200°C. In fact no thermic event is detected in the considered interval of temperature and in particular in correspondance with the melting temperature of the NCX 1022.

EXAMPLE 9

Determination of the dissolution speed of the solid dispersion of NCX 1022

The dissolution rate of the active ingredient from the solid dispersion produced in Example 6 has been compared with the dissolution rate of the pure active ingredient, using the paddle method described in F.U.X. In detail, 40 mg of the solid dispersion or 5 mg of pure NCX 1022 have been placed in a thermostated container at 37°C±0.5°C in 500 ml of distilled water including 1% w/v of Tween 80 and kept under stirring at 100 rpm. The quantity of NCX 1022 dissolved has been spectrophotometrically determined in continuous at a wavelength of 240 nm.

The following table shows the average of the results obtained from three determinations, expressed as percentage of ingredient dissolved at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion
5	4.05	45.56
10	3.91	49.73
15	3.86	50.36
20	3.81	49.90
25	3.91	48.84
30	3.77	47.18
35	3.91	45.60
40	3.77	43.71
45	4.09	41.93
50	4.33	40.2
55	4.23	38.82
60	4.32	37.18

The results obtained show that, even if the solubility of the pure active principle almost null, with a solubilisation of only 4.3% within one hour, when this is in form of a solid dispersion in polyvinyl pyrrolidone its dissolution rate and therefore its apparent solubility remarkably increase and it is possible to obtain the release of 50% of active ingredient in less than 15 minutes.

CLAIMS

1. Solid dispersions comprising at least one nitrate active ingredient and one hydrophilic polymer chosen among cellulose ether, polyvinyl pyrrolidone, polyethylene glycol.

2. Dispersions according to claim 1 wherein said polymer is polyvinyl pyrrolidone .

3. Dispersions according to claim 1 wherein said cellulose ether is hydroxypropylmethylcellulose and it has a molecular weight such that the viscosity at 20°C of a 2% solution in water is lower than 50 cps.

4. Dispersions according to claim 1 wherein polyvinyl pyrrolidone has an average molecular weight comprised between the molecular weight of polyvinyl pyrrolidone K17 and the molecular weight of polyvinyl pyrrolidone K30.

5. Dispersions according to claim 1 wherein polyethylene glycol has an average molecular weight higher than or equal to the molecular weight of polyethylene glycol 1000.

6. Dispersions according to claim 1 wherein said active ingredient is contained in amounts ranging from 10% to 50% w/w and said hydrophilic polymer is contained in amounts ranging from 50% to 90%.

7. Dispersions according to claim 6 wherein the amount of said active ingredient is between 15% and 40% w/w.

8. Dispersions according to claim 6 wherein the amount of said hydrophilic polymer is between 60% and 85%.

9. Dispersions according to claim 1 further comprising pharmaceutically acceptable excipients.

10. Dispersions according to claim 9 wherein said excipients are contained amounts comprised between 2% and 20%.

11. Dispersions according to claim 9 wherein said pharmaceutically acceptable excipients are chosen from the group consisting of wetting and solubilising agents.

12. Dispersions according to claim 11 wherein said solubilising agents are surfactants.

13. Dispersions according to claim 12 wherein said surfactants are chosen from the group comprising polysorbates, esters and ethers of polyethylene glycols, polyhydroxylated castor oil and sodiumlauryl sulphate.

14. Pharmaceutical formulations for oral, rectal, parenteral, transcutaneous, transmucosal administration of active principles comprising the solid dispersions according to claims 1 to 13.

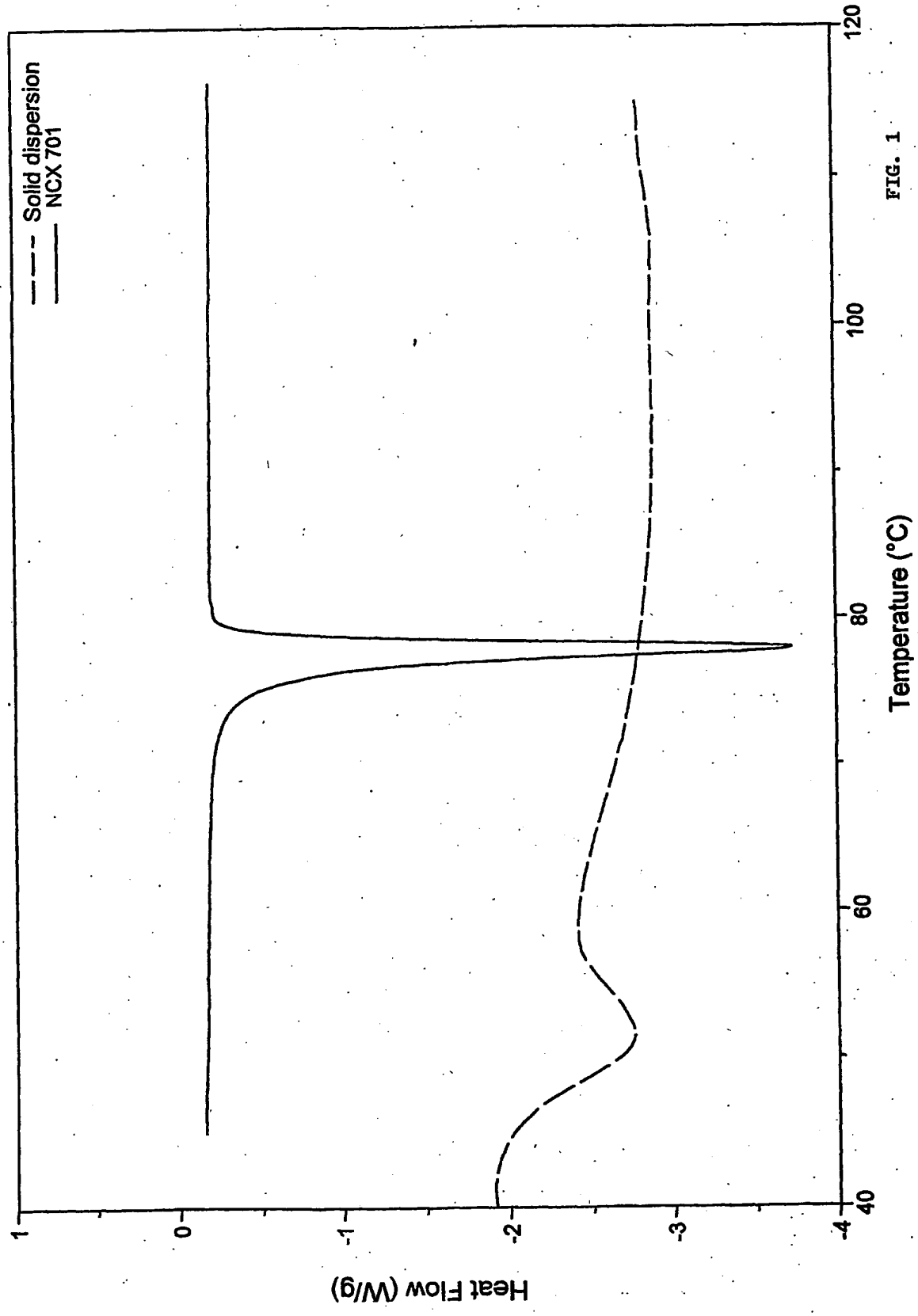

Solid dispersion
NCX 701
Heat Flow (W/g)
1
0
-1
-2
-3
-4
Temperature (°C)
40
60
80
100
120

FIG. 1

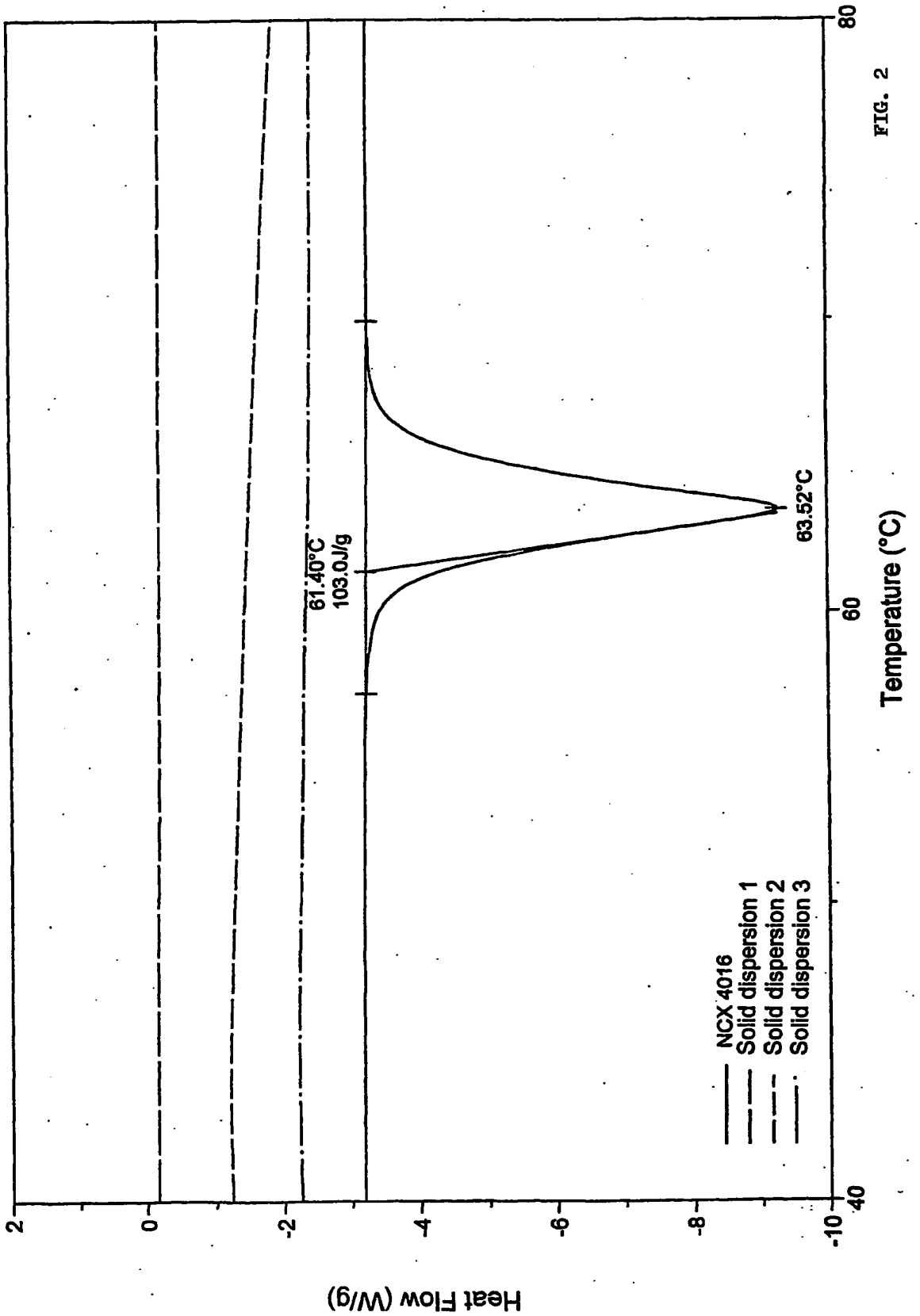

Heat Flow (W/g)
2
0
-2
-4
-6
-8
-10
Temperature (°C)
40
60
80
61.40°C
103.0J/g
63.52°C
NCX 4016
Solid dispersion 1
Solid dispersion 2
Solid dispersion 3

FIG. 2

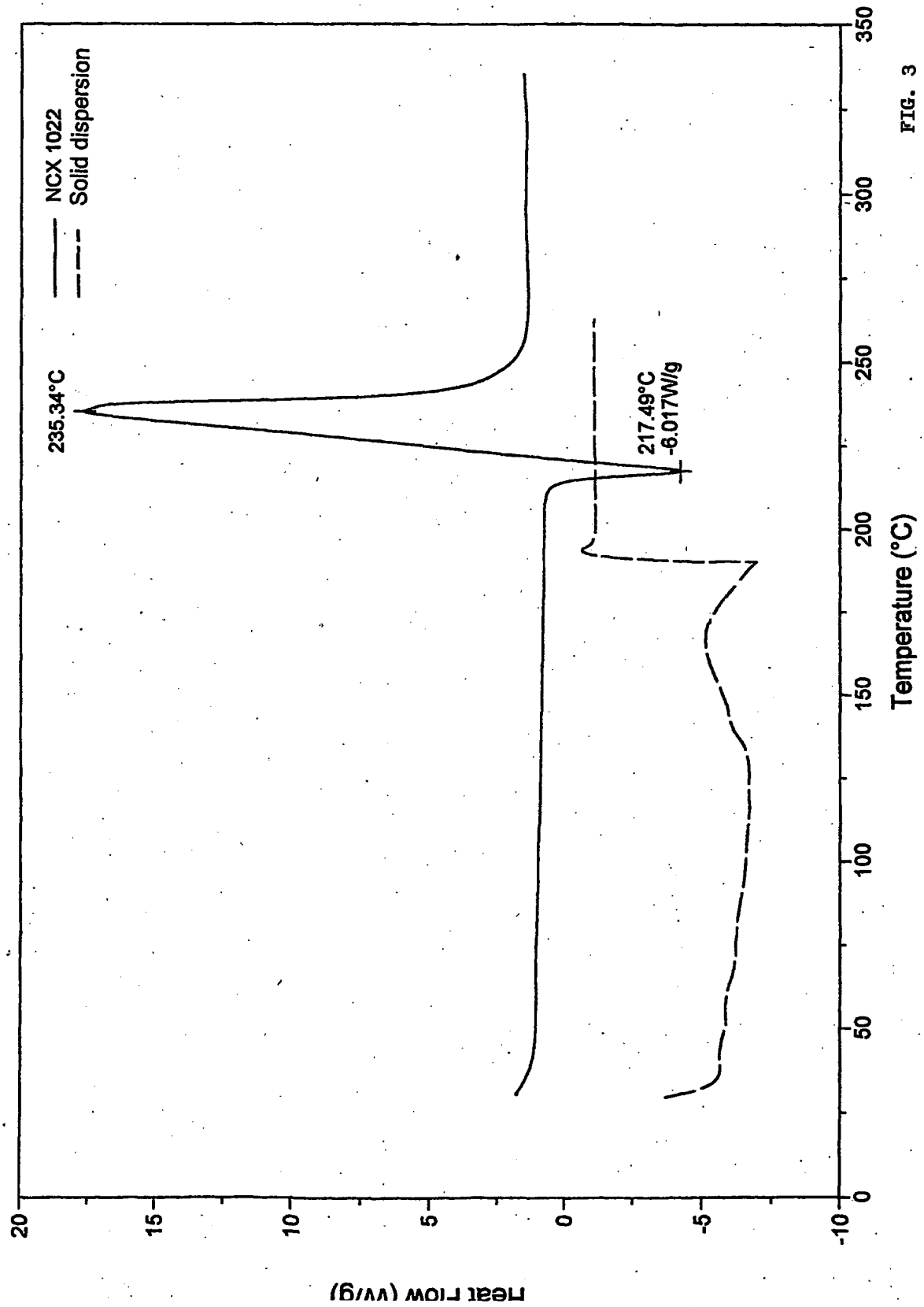

NCX 1022
Solid dispersion
235.34°C
217.49°C
-6.017W/g
Heat Flow (W/g)
Temperature (°C)
20
15
10
5
0
-5
-10
0
50
100
150
200
250
300
350

FIG. 3

INTERNATIONAL SEARCH REPORT

Ir I Application No
PCT/EP 01/14967

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MINGHETTI, P.; ET AL.: "Application of solubility parameter in nitroflurbiprofen topical semisolid formulations" PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 27TH, 7 - 13 July 2000, pages 936-937, XP002199487 Paris (FR)	1,5,9,14
Y	page 936; example 2; table 1	1
P,Y	WO 01 15677 A (ALCON LABORATORIES) 8 March 2001 (2001-03-08) claims 1,7,10,11 page 10, line 6 - line 17 page 14, line 1 - line 8	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2002	06/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]nal Application No
PCT/EP 01/14967

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0115677 A	08-03-2001	AU 6917400 A	26-03-2001
		WO 0115677 A2	08-03-2001